Immune Systems, AIDS, and Bird Flu

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Drastic changes have occurred in the human condition over the last hundred years. Many have been positive, but others have resulted in a breakdown of the barriers that keep non-human microbes from being able to infect humans, or that keep sporadic cases of human infection from being able to spread efficiently enough to become established as new, self-perpetuating human diseases. The most important new disease we have so far gotten through this breakdown is AIDS. But AIDS is a bootstrap: it will itself enable the transfer of further new diseases. The most serious immediate risk is probably from bird flu; but other immunodeficiency viruses transferred via AIDS, and via other means that have only arisen, or have become much worse, over the last hundred years, may present an even greater long-term danger.

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A note to the reader

This is a very long piece (79,000 words, as long as a short book) but my contention is that whatever considerable demands on your time it would require are vastly outweighed by the importance of its subject matter, and by the fact that most aspects of this subject have never been adequately dealt with before – indeed the most important of them have scarcely been dealt with at all. The Abstract should provide you with enough information to decide whether beginning this project is worthwhile. If the answer is "Yes," then I have written a short accompanying piece (which I can more easily keep updated than this rather unwieldy one) containing a few reading suggestions, as well as some other information, such as corrections not yet applied, contact information, problems with certain browsers (Internet Explorer seems to work fine; Firefox prior to 3.6 does not), and additional download links for the PDF version of the file, in case the two listed above cease to function. Also, comments can be left there. You can access this related article at http://alberttelfordsson.wordpress.com/2012/04/28/further-information-about-immune-systems-aids-and.

Abstract

This paper consists of several separate but interrelated ideas having to do with AIDS and immune systems.

1) There are many ways in which AIDS will sicken and kill people who never become infected with HIV. A simple example would be a non-HIV-infected person who catches tuberculosis from someone who has come down with TB as a result of immune-system compromise due to AIDS. There are many other examples, some likely to produce far more deaths, and some which will remain, even if HIV is one day exterminated, continuing to kill for as long as the human race persists. It is not possible to say, or even to intelligently estimate, whether HIV will kill more people directly or indirectly.

2) AIDS mounts an attack against the immune system of the species as well as against the immune system of the individual. There are important parallels between the two attacks. Just as the weakened individual immune system of AIDS victims allows their bodies to become infected by organisms that could not otherwise succeed, so too the weakened species immune system will allow the human race to become host to new pathogens that have never before been able to infect our species; and it will be the general population, not just those with AIDS, who will fall victim. This may be the most likely route for a pandemic strain of bird flu to enter the race. If it occurs, far more people could die within a year from bird flu than have died of AIDS to date. This all by itself justifies the last sentence of point 1, above.

3) It is my view that most estimates of potential bird flu deaths are much too low, as a result of the failure to take into account certain key points. I will discuss several such points.

4) It is useful to give a broader-than-usual definition in discussing immune systems. Insights will thereby emerge.

5) Transfusion (which bypasses one of the most important components of the immune system, the skin), transplants, several other medical procedures, and several nonmedical recent changes to human society contribute to the injury to the species immune system. Some of these further contributions are quite major.

6) Both AIDS cases and these other injuries may have effects on existing human diseases, allowing additional evolutionary potentials to emerge, perhaps, especially, new means of spreading.

7) I have included a detailed appendix arguing against the popular view that very deadly pathogens have to moderate their virulence before they can cause widespread epidemics (else they kill their hosts before they can infect further hosts). I think this is wishful thinking.

Most of the arguments in this paper are based on natural selection. By and large they are simple enough that any intelligent person, even one with no scientific background, should be able to understand them. I have devoted a great amount of effort to this end. I think I have been successful, at least for all the key points. If this means specialists are required to read a few passages they already know only too well, I apologize.

Keywords: Cross-species transfer, Species immune system, Emerging diseases, Avian influenza, 1918 pandemic, Evolution of virulence

1. The two immune systems

1.1. The individual immune system

When we speak of the human immune system, we ordinarily mean the immune system that exists within each individual human body and which serves to keep out or to control the myriad noxious pathogens – the *sea* of noxious pathogens – within which we live and breathe. Included within this immune system are, first of all, various physical barriers such as the skin and mucous membranes, the peritoneal and other membranes, the cranium, the blood-brain barrier, and whatever other barriers exist within the body that serve as impediments to the spread of infection. Secondly, and somewhat akin, are other physical mechanisms for removing these pathogens: the ciliated cells of the respiratory tract that sweep microbes and dust particles upward and out of the lungs; vomiting and diarrhea when we get a gastrointestinal infection; the mucus production of the nasal passages that gives us a runny nose when we catch cold, as well as others. Thirdly, there are the several types of white blood cells which kill invading organisms by eating them or by producing generalized poisons. Included here is also the system that produces and mobilizes these cells. Fourth are the antibody-producing cells which generate poisons that affect only the specific pathogen they are designed for, and the system that underlies them. Fifth are the various body fluids that have germicidal properties, such as tears, saliva, stomach acid, and mother's milk and colostrum, whereby antibodies are transferred to the newborn. And there are other components that also belong within the standard picture.

I would like to extend this standard picture of the immune system somewhat to include *everything* that keeps infection out of the individual, or, failing that, extirpates it with minimal damage, or, failing that, keeps it under control, or, failing that, at least slows its progress. This larger definition would include other "friendly" organisms, such as those that live within the gut, mouth, and vagina, which do much to keep out the less-friendly organisms. If this part of our immune system is destroyed, for example by antibiotics, we may face an onslaught of yeast or *Clostridium difficile* or a urinary-tract-infecting strain of *E. coli.* Similarly, there are organisms that live on the skin that help to keep the more pathogenic organisms in check. In other species, these friendly skin organisms may be much larger than bacteria. Thus, on this view, tick birds are part of the immune system of the rhinoceros.

For humans and their domestic animals, there is a most important addition to this extended immune system. I mean the human inventions such as antiseptics, vaccines, antibiotics, and drugs that keep infection out of the body, extirpate it once it is there, or at least keep it under control or slow down its progress. The entire medical system – doctors, nurses, hospitals, annual physicals, ambulances, elaborate equipment, medical insurance, legislation relating to health matters, etc., etc. – can also be included here. The current human population is far too large and densely packed to be able to survive without these human extensions to our immune system. If they all suddenly vanished, most of us would also vanish shortly thereafter.

Of course, there is a trivial sense in which virtually *everything* affects everything else, so that under the definition as I have just given it, virtually everything is either a part of the

immune system or what might be called the anti-immune system. I do not know where to draw the line, but it seems clear that at least some of the things listed above, such as the vaccines, antibiotics, and antiseptics, need to be logically included within the definition of the individual human immune system.

1.2. The species immune system

But there is also another immune system, that of the species as opposed to the individual. By analogy with my extended definition of the individual immune system, the species immune system consists of everything serving to keep noxious organisms from being able to infect our species, or, failing that, clears the infection from our species once it has occurred, or, failing that, minimizes the numbers infected, or, failing that, slows down the progress of the infection. We don't have to worry about the terrible ravages of rinderpest or Marek's disease, except as to their effect on our cattle or poultry. They do not infect human beings. Our species immune system keeps them out.

Our species immune system does not keep out rabies. And our individual immune system is helpless against it: if we catch it, we will almost surely die. But we will not often spread it to even one other person, so that, again, while the individual dies, the species is protected, and the focus of infection which overwhelmed one individual body is quickly vanquished from the race.

Our species immune system does not keep out Ebola. If we catch it, we are very likely to die. We are also very likely to spread it onward. But, so far at least, the spread has been quite limited and short-lived. Quickly, the last infected individual has either died or recovered, and once again, Ebola has been eliminated from the human race – another success for our species immune system.

There are several million animal species on the planet, and every one of them has hundreds, if not thousands, of pathogens that may infect it. Some of these pathogens can infect many other animal species as well. But many are specific for that one species, or that one species and a few closely-related others. The total number of potential pathogens is therefore legion, but only a minuscule portion are able to infect any one species. Without a very efficient species immune system, no species could survive.

1.2.1. Elements of the species immune system

1.2.1.1. Four types of gaps

It is useful to consider some of the elements of this other immune system.

First, and perhaps most important of all, are the gaps that separate species. These gaps represent hurdles which organisms that dwell in one species must leap in order to enter another. The larger the gap, the better the protection. Anything that diminishes the gap, lowers the species immunity.

The various gaps occur in at least four different forms.

1) A spatial gap occurring as a result of different habitats. We have not had to worry much about monkeypox in the past, because human habitats, at least those densely-peopled habitats where monkeypox might be likely to efficiently spread, have not encroached much on the monkey habitats where the disease occurs. With ever-increasing human population pushing further and further into remote territories, this aspect of species immunity may be lessening. On the other hand, we are exterminating indigenous species as we encroach, and in some cases this may be strengthening our species immune system.

2) A spatial gap occurring as a result of geographic barriers. Old World inhabitants did not have to worry about pathogenic organisms occurring in the New World, and vice versa, until that geographic gap was closed. In today's world of easy travel, this gap is so diminished as to scarcely exist at all. As a result, there has been a significant decline in our species immune system.

3) A time gap. We do not have to worry about 1918 flu, because that was 1918, and this is now. There is no 1918 flu to cause another epidemic. Or, rather, that was true until recently. But now that scientists have artificially reconstructed the 1918 flu, the time gap for this very serious pathogen has been eliminated, and we are again at risk. A simple, common laboratory accident could once again unleash one of the greatest killers of history. It would likely kill far more this time, due to our far greater population, which provides not only more fodder but better fodder. Not only the population but its density has greatly increased since 1918. More about this later.

The scientists who resurrected the 1918 flu say that it will help them understand and combat flus in general. With the looming danger of bird flu, this is an important consideration, and if they are very, very, very careful, it is possible they will in the long run do more to enhance species immunity than they have already done to reduce it. But they have done a lot to reduce it. Except for the ideas below that argue that AIDS is likely to usher bird flu into our midst, I would consider a 1918 flu epidemic now more likely than an epidemic of the current, deadly bird flu. Laboratory accidents are very common, and in this case could be extraordinarily tragic. At least one laboratory worker has contracted smallpox (and died), since its complete eradication in the wild. At least three escapes of the SARS virus have occurred from facilities with safety standards only slightly less than those being used to confine the 1918 flu (MacKenzie, 2004; von Bubnoff, 2005). Flu is more contagious than smallpox and far more contagious than SARS. Here is a quote from John M. Barry's excellent book, *The Great Influenza*. He is describing the introduction of the disease into Philadelphia in 1918 (Barry, 2004, p. 3):

> This same disease had erupted ten days earlier at a navy facility in Boston. Lieutenant Commander Milton Rosenau at the Chelsea Naval Hospital there had certainly communicated to [Paul A.] Lewis, whom he knew well, about it. Rosenau too was a scientist who had chosen to leave a Harvard professorship for the navy when the United States entered the war, and his textbook on public health was called "The Bible" by both army and navy military doctors.
>
> Philadelphia navy authorities had taken Rosenau's warnings seriously, especially since a detachment of sailors had just arrived from Boston, and they had made preparations to isolate any ill sailors should an outbreak occur. They had been confident that isolation would control it.

> Yet four days after that Boston detachment arrived, nineteen sailors in Philadelphia were hospitalized with what looked like the same disease. Despite their immediate isolation and that of everyone with whom they had had contact, eighty-seven sailors were hospitalized the next day. They and their contacts were again isolated. But two days later, six hundred men were hospitalized with this strange disease....

Flu is among the most difficult of all diseases to control, because it spreads so rapidly and is contagious even before victims begin to feel any symptoms. Within a few days of this episode, the first deaths began in Philadelphia: None for the week ending 28 September. Then 706 for the first week of October. Of the city's ultimate total of 16,000 deaths, more than 10,000 occurred during the next three weeks (Crosby, 1989, p. 60). The medical system was overwhelmed. Many victims never saw a doctor or a nurse. Some died within 24 hours of their first symptoms. Indeed, "Charles-Edward Winslow, a prominent epidemiologist and professor at Yale, noted, 'We have had a number of cases where people were perfectly healthy and died within twelve hours'" (Barry, 2004, p. 242). Unlike other flu epidemics, the greatest mortality occurred among healthy young adults.

The 1918 flu killed more people within three months than World War I killed in its four years, soldiers and civilians alike, on both sides [1]. And the limited medical progress we have made against it, and the better progress against the bacterial pneumonias that often followed in its wake, will avail us nothing if we never get to see a doctor or nurse. It is simply unbelievable that this plague should be handled at any less than the maximum containment facility in existence, much less that it should be permitted at multiple locations whose security is up to the scientists' own judgment.

4) The gaps that are represented by the genetic differences between species. There is a plethora of life and a shortage of resources. All species produce more, and nearly all produce *far* more, offspring than can possibly survive. The maximum number of offspring that can possibly survive, when averaged over any reasonably long time period, is one for an asexual species and two for a sexual species. This is a sweeping and crucially important fact, one of the most important facts in all of science. No educated person should be unaware of it, yet the vast majority are, including many professionals in the life sciences. The reasoning behind it is even more important than the fact itself, and fortunately, unlike the case of another of the most sweeping and important facts in all of science, $E = Mc^2$, which only a few people in the world understand well enough to know firsthand whether it is right or wrong (we are forced to take the word of experts), in this current case the reasoning is simple and can be seen to be true by anyone who can multiply and divide. Moreover, the demonstration takes only a few lines and is well worth a brief digression.

Consider a sexual species and what would happen if instead of two surviving offspring, it averaged four. We must count offspring carefully and specify what we mean by surviving: Let us say we mean surviving long enough to reach reproductive age. Let us assume this is a typical species with roughly equal numbers of males and females. If each female of the current generation living long enough to reach reproductive age (and those are the only ones who reproduce) gives rise to an average of four offspring who live long enough to reach reproductive age, then on average two of these four will be female. Each female surviving to reproductive age in the one generation is replaced by two females surviving to reproductive age in the next. The number of surviving females (and indeed the population as a whole), is doubling with every generation. Each 10 doublings represents a

1024-fold increase. (Start with 1. One doubling gives 2. Two doublings give 4. Then we have 8, 16, 32, 64, 128, 256, 512, and finally, after 10 doublings, 1024.) If we round 1024 off to 1000, then we see that after another 10 doublings, each of that 1000 will have grown another 1000 times, for a million-fold increase after 20 doublings. After 40 doublings, which is only 40 generations, the population will have increased one trillion fold (i.e., one million million times). For nearly all species, a trillion-fold population increase is absurd. And 40 generations is but an eyeblink in the existence of most species.

Quite obviously, over any very long time span, instead of four surviving offspring, the number must be very close to two. Each female of the one generation will average only one replacement female in the next. Of course, we must count offspring per lifetime. If a fox produces four pups at a time, one must add up all the times the fox gives birth. If it gives birth three times, then there are 12 offspring, 10 of which on average will die before reaching reproductive age. This is true if we are correctly counting the number of births of an average female fox who lives to reproductive age. We must count foxes who never give birth at all (perhaps because they die the day after reaching reproductive age) as producing zero offspring.

This is a very high mortality, but consider insects, worms, or fish, which produce hundreds, thousands, even millions of offspring. A female salmon lays several million eggs, yet only two of them on average will survive to reach reproductive age. Often it is stated that the reason so many offspring are produced is that it is required because the mortality is so high. This is almost always exactly backwards. The reason mortality is so high is because huge numbers of offspring are produced when there are sufficient resources available to keep only two, on average, alive. And, of course, when we are dealing with asexual species, similar arguments will show that instead of two, the number surviving to reproductive age is only one [2].

There is, therefore, a continuous, unremitting pressure of life attempting to expand beyond the limits of the resources required for life (several millions of salmon crowded into a space that can support only two) – a literal life-and-death competition for the vastly insufficient necessities of existence. No matter how great the resources, we lifeforms will produce so many offspring as to fill our niche completely full and then to overflow. If we do not, our "prudent" genes will be crowded out by our more ruthless competitors in this unwinnable race: At the beginning of the race, those who reproduce more than average increase the tendency to overreproduction through the propagation of their imprudent genes, while those who reproduce less than average *likewise increase* the tendency to overreproduction through the removal of their prudent genes. In the end the tendency to overreproduction must continually increase until finally checked through extremes of reproduction so great that adding still more offspring results in fewer, not more, survivors; and this point is not reached in certain species until the extremes of profligacy above are achieved, with 99+ percent deaths, and in no single species that I am aware of until more than half of all offspring are borne only to die before maturity (and this is true of our own species, too, if one goes back a few thousand years, and not just a few hundred, when the industrial revolution suddenly expanded the temporary carrying capacity ten-fold, a capacity we have still not *quite* filled up to overflowing) [3].

Having now convincingly (I hope) made this point, we can apply it to the last of the four kinds of gaps – the genetic gap – that I have listed as together constituting the first element of the species immune system.

Each very particular strain of pathogen must compete for its life against other strains

which are almost identical but slightly different. If the slightly-different strain is more highly specialized to exploit its particular environment – its particular host species – it will likely outcompete, and ultimately eliminate, its rival. Thus, there is a strong pressure for each pathogen to specialize in a single host species, or in a few closely-related species. Otherwise, there is an opening for a variant that is more specialized, one that devotes *all* its resources, and not just 99 percent, to optimizing its infection of its most favored target. And in this crowded world, openings are almost always ultimately filled.

Thus, the gaps that exist between two host species are mirrored by gaps between their pathogens. A pathogen of one host will not be likely to jump the gap and set up an infection in another host, unless the two hosts are very similar, with only a minimal gap separating them. And even if it does manage to jump to one or a few individuals of the other species, it is likely the similar pathogens of the new species, presumably much more highly adapted to infect it, will outcompete and eliminate it.

Somewhat oddly, perhaps, that means that the native pathogens of a species are part of its species immune system. Without them to outcompete their relatives from other species, it is likely many more successful jumps would occur. (Often, they did occur, *once*, and after adapting to their new host, evolved into the pathogen that now keeps its relatives in the first species from successfully jumping again.) Another reason we did not in the past have to worry about monkeypox is that our own smallpox kept it out. Now, with neither natural smallpox nor smallpox vaccine to provide any immunity to monkeypox, it is far more likely to make the jump and survive to become a new human pathogen.

1.2.1.2. Herd immunity

The second element of the species immune system is something that is sometimes called herd immunity. After the 1918 flu, the susceptible part of the population had largely been either killed or immunized against future infection. With its fodder now consumed, the virus died out. But without the virus to maintain it, the herd immunity is also dying; and with the youngest of the survivors (whose immunity is probably less than complete anyway) now around 90 years old, the herd immunity against this particular virus is almost gone.

This is related to population. Many estimates have been made of how large the human population had to be in order for smallpox or measles or the other great infectious diseases to persist as a human infection. In the case of measles, for example, a population of at least 250,000-400,000 is required (Keeling and Grenfell, 1997). With the small population of prehistoric times, many of the great diseases of history could not have survived. Just as with the 1918 flu, they would have consumed all the susceptibles and died out. It requires a large population, different for each disease, to be able to keep the disease always circulating somewhere and never completely dying out.

Here we harken back to the gaps. In a society consisting of small tribes with limited contact with neighboring tribes, even a large population might prove impossible for a new pathogen to invade. Even in modern society, with its 7 billion people, there are still jungle tribes with limited contact with the rest of the world. In the case of Ebola, Lassa, and probably many other potential pathogens (most of which we are unlikely even to be aware of), these isolated tribes are precisely the likely entry point. The reason at least some of

these pathogens have never successfully invaded our species is almost surely *not* that they could not infect modern society, but that they could not infect the small, pre-modern societies, full of gaps, which is the only type they encountered. If they ever make it out to the rest of the world, some of them, at least, will likely do just fine. The difference between a small jungle tribe of a few hundred people and modern society with its billions is gigantic. *Many* pathogens that could never survive in the former environment can easily colonize the latter. But first, they must bridge the gap from the remote jungle tribe to the rest of us. That gap is what is protecting us.

With modern travel and tourism, the isolation is rapidly diminishing. The gaps that have protected us are largely history. It is likely several new diseases will emerge with the closing of this gap. If Ebola or Lassa are among them, this will be a world-changing event.

Vaccines can certainly strengthen herd immunity. Thus they are not only part of the immune system of the individual, but also the immune system of the species. Indeed, most things that strengthen individual immunity can be thought of as strengthening herd immunity, and thus (with some notable exceptions [4]) the entire individual immune system and the components that make it up, are part of the species immune system. Indeed, as we shall see later in this paper, they may well be the most important part of all.

1.2.1.3. Social organization

The third aspect of species immunity is social organization. Consider the solitary life of the mountain lion as contrasted with that of the caribou, a species which lives in large herds. There are many disadvantages to the solitary life, but one advantage is the serious impediment it presents to the spread of diseases.

Social organization plays a much larger role in our own species immune system than it does in the case of most non-human animals. Examples are public health services, epidemiological surveillance systems, educational efforts that promote health or, in a case such as AIDS, reduce chances of acquiring a certain disease, quarantine laws meant to prevent known infected persons from spreading their infection, quarantine laws (nowadays mainly dealing with agriculture or pets rather than people) that sequester all potentially infected individuals until sufficient time has passed or tests have been conducted to conclude they are not infected. There is also the ultimate form of quarantine which forbids certain species from being imported at all (sometimes for the damage they may do themselves; other times for the diseases they may carry).

In my view, quarantine is an extremely efficient means of stopping, or slowing the spread of, infections. In a case such as bird flu, even slowing by a factor of two might give enough time to perfect or produce a vaccine, and thereby save many millions of lives. It could also allow time for recoveries, people now immune who could safely care for those infected, or safely continue their other vital social functions, thereby saving many more lives.

Many authors have pooh-poohed quarantine attempts in the face of the flu, saying they were ineffective in 1918. In the first place, this claim flies in the face of all reason. Quarantine *has* to make a difference, and studies claiming otherwise are either faulty or else the quarantine was faulty. In the second place, it is not true: In 1918 Western Samoa suffered among the highest death rates in the world. Within a few months, 22 percent of its

population was dead. But a strict quarantine kept the disease out of nearby American Samoa, and not a single person died of flu (Barry, 2004, p. 364). In 2001, a sudden 27 percent decrease in air travel due to the 9/11 terrorist attacks, delayed the normal flu season by about 13 days in the U.S. In France, where there was no such reduction, there was no delay. This small delay may seem insignificant, but if a bird flu pandemic emerges, contagious and deadly enough to kill hundreds of millions around the world, as is certainly entirely possible, then at its height there will be several million people dying per day. If a country sees such an unstoppable catastrophe occurring elsewhere in the world and realizes it is only a matter of days or weeks before its own people will be dying like flies, then it is possible to do an awful lot of preparation in 13 days. Last-minute measures undertaken both by governments to protect their citizens and individuals to protect themselves can accomplish a lot. And the 9/11 air travel restrictions were not designed to slow the spread of infection, indicating that perhaps significantly more than 13 days' delay might be possible (Brownstein et al., 2006).

Recently, an important paper in *JAMA* (Markel et al., 2007) studied 43 U.S. cities and found that those that instituted the most stringent measures in 1918 fared significantly better than those cities that did not. Moreover, relaxation of the measures frequently led to a resurgence of cases.

But quarantine tramples on individual rights, and for that reason has gotten so much bad press that this particular weapon in our species immune system may be almost useless. If that is so, it represents a significant weakening of the system as a whole.

In January 2006 I heard a radio interview with the author of a new book on the leprosy colony on Molokai (Tayman, 2006) [5]. He maintained that leprosy was so minimally infectious that the quarantining of patients, at least for the most part, had been pointless and wrongheaded and just one more exercise in the long history of man's inhumanity to man.

I didn't know a great deal about leprosy, but I immediately thought of several strong objections to this view:

First of all is the point that in an important sense – in the very sense that is relevant here – *all* established human diseases are equally transmissible. In every case, over the long term, one infected person infects on average almost exactly one further person. When conditions are especially favorable, but for a limited time only, one person may infect more than one further person. But this will be followed by a period in which one person is infecting less than one, or, at the very most, one person. Any other conclusion is absurd. If each person infects two others, in 20 generations of spread, which in the case of flu may be only a couple of months, each infected person will have infected a million more. For flu, this is indeed possible; but 40 generations of spread, less than half a year, would require a multiplication by one trillion, and we see the absurdity full on.

Similarly, if each person infects only 1/2 further person on average, then within 40 generations the infection will be one-trillionth its former level, and again we see the absurdity of a transmission rate significantly different from 1.0 over a period any longer than, at most, 200 or 300 generations of spread [6]. Leprosy *appears* to be much less transmissible than gonorrhea, because it takes years for a person with leprosy to pass his one case on, versus days or weeks in the case of gonorrhea. But, despite its relative slowness, leprosy has certainly been around for more than 200 or 300 generations of spread, and its transmission rate has certainly averaged close to 1.0.

If a formerly-quarantined leprosy victim is allowed to interact freely with the rest of the population, then if his rate of contact with other people is doubled, it is likely he will spread

his infection to roughly twice as many people: two instead of one. Since the severe quarantine traditionally applied to leprosy victims likely diminished their contact with the rest of the population by far more than a factor of two, it is likely such a change in quarantine would result in a transmission rate of even more than two.

But, since it is more than enough to make my case, I will assume that removing the quarantine would change the transmission rate from 1.0 to 2.0.

If this merely meant a doubling of infections, then the author of the leprosy book would need to make a case as to why subjecting twice as many people to this terrible disease was not worse than quarantining half that number. The quarantining was extremely onerous, so *perhaps* he could indeed make a valid case. But he has to do much more, for cases are likely to far more than double.

If each individual with a given disease infects on average two further individuals, then cases will grow, doubling with each generation of infection, until limits are reached or conditions change to bring the infection rate back down to 1 or below. In this case, the change in conditions may well be the reimposition of quarantine. But the opponent of quarantine can hardly advocate its temporary removal from a few to be followed by its reimposition onto many more (and with extra cases of the disease, besides). The opponent cannot consider this measure and must instead estimate the ultimate size of the epidemic in the absence of quarantine. And it is clear that cases will continue to grow until the most susceptible pool is exhausted, and the next most, and the next most, until what is left is a pool which is only half as susceptible as the original. Instead of each case infecting two others, as it does when the quarantine is first removed, all the easy targets have been consumed and what is left permits only one infection.

At that point, cases cease to grow; but it is clear that depending on the nature of the gradient, and the number of cases that was stable under quarantine, cases are likely to far more than double. In the case of a disease such as leprosy, which is quite rare, it is possible that removal of the quarantine would multiply the stable number of cases by a factor of 10 or even 100. The author must explain why subjecting 10 or 100 times as many to this terrible disease is better than quarantining the few rare cases. And that is what he must do if the transmission rate is merely doubled, when in fact it will likely increase by a significantly greater factor.

Regardless of the relative strength of the arguments, it is a fact that discussion of quarantine raises such heated opposition that it is unlikely we will anytime soon have it back within the armamentarium of our species immune system. To the (probably large) extent that this strong opposition to quarantine is due to the AIDS epidemic, if millions of extra deaths occur from a bird flu or some other epidemic as a result of the unavailability of quarantine, these too must be added to the indirect deaths due to AIDS. The mechanism involves the diminishing of the species immune system.

One final point with regard to quarantine: logically, it works as well for uninfected individuals to quarantine themselves as it does for them to quarantine the infected. In a case of a rapidly-moving generalized pandemic, as might be expected from the flu, it might work much better. People can lock themselves in their houses until the scourge has passed. Instead of having to force reluctant infected people into quarantine, this has the advantage of dealing with willing subjects who *want* to be quarantined, indeed who will do it to themselves, all by themselves. No doubt the human rights advocates will like this version much better. But why it is less restrictive of human rights for government to enforce quarantine with laws and imprisonment than for a disease to enforce it with the death

penalty still needs to be explained. Moreover, the numbers forced into quarantine by the government would normally be a tiny fraction of those forced into quarantine by the disease.

Basically, self-quarantine is a fallback position the individual can do if society fails, whether from lack of quarantine or lack of vaccine or whatever, to prevent a generalized outbreak. It would be extremely inefficient to quarantine the rest of society in order to protect them from a handful of infected people. And it would not work, because the incentive for self-imposed quarantine would not be sufficient to get all the uninfected to sequester themselves, not when there are only a handful of cases. The infection would grow until it reached the point that a large fraction of the uninfected were too frightened not to participate. The incipient infection that could have been stopped with a strict quarantine of the handful of infected, will have to grow into a much larger epidemic before this will occur.

I am not a big supporter of individual human rights, not at any rate the kind that puts individual liberties above important social goods (and most certainly not when their enforcement in favor of a handful of individuals might cause tens of millions of deaths to innocent people, who are also individuals and who also have human rights). Therefore this is an easy question for me. But it is my belief that even the most ardent advocates for human rights would come to similar conclusions if they would but think about the pros and cons with due care.

2. Indirect deaths due to AIDS

I think I have now elucidated enough of the basic ideas regarding the two immune systems to be able to proceed to the most important part of this paper. It begins with a list of ways in which AIDS will kill those who never become infected with HIV.

2.1. Non-opportunistic diseases in AIDS patients

The most obvious of these is the infection of AIDS victims by diseases, notably tuberculosis, that can sicken and kill those without either AIDS or HIV. AIDS victims are more likely to become infected with the tuberculosis organism, and once infected, far more likely to develop active, transmissible TB, than people without AIDS (Morens et al., 2004; Markowitz et al., 1997; Centers for Disease Control and Prevention, 1991). Over time, there will be millions of extra TB cases in the world due to non-HIV-carrying people becoming infected by those who have developed TB as a result of AIDS. Moreover, these non-HIV TB cases will infect others, and these too would not have occurred but for AIDS. Some fraction of these cases will die. I do not know the magnitude, but it will clearly amount at least to thousands of deaths per year to non-HIV-infected people indirectly killed by AIDS [7].

2.2 Shortening the useful life of antibiotics

The second way in which AIDS may kill those without HIV is far more important, and indeed may significantly increase the deaths due to TB and whatever other diseases belong in the first category.

AIDS will greatly shorten the useful life of antibiotics – for everyone, not merely AIDS victims – and it will do this by breeding antibiotic-resistant strains of TB and many other diseases. These antibiotic-resistant strains of TB will kill a far greater portion of non-HIV-infected TB victims than will the normal TB strains (though not in the very poorest areas of the world, where typical TB victims receive no treatment anyway). And those who catch their TB from an AIDS victim will have a far greater chance of getting (and passing on) a resistant strain than those who catch it through the traditional route.

The mechanism by which resistance will develop is surely evident: AIDS victims fall prey to a great variety of infections. To begin with, when their AIDS is not yet too severe, most of these infections (the non-viral ones, at any rate) can be eradicated with a strong course of antibiotics. But as the deterioration of the immune system progresses, it becomes more and more difficult to completely eradicate the opportunistic infections. In the end, the treatment fails to cure the patient and he dies of his infections, which by that point have been much exposed to quite probably multiple courses of multiple antibiotics. Some measure of resistance will have developed. If someone else, especially if another AIDS patient, catches this partially-resistant organism, it will progress further in its path to resistance. Because of the vastly greater use of antibiotics in treating AIDS patients, and because of the vastly greater number of antibiotic failures, and because other AIDS patients are much more susceptible to acquiring the products of these antibiotic failures (and may be housed together in conditions that do little to prevent such spread), the rate at which resistant infections develop among AIDS patients will be multiplied many times over the rate at which this serious problem is already occurring among the general, non-HIV-infected population. The useful life of antibiotic drugs is being greatly shortened for all of us, due to AIDS. And even if AIDS is one day entirely eradicated, deaths from diseases that were once readily curable but now no longer are, will continue indefinitely.

Perhaps other antibiotics will come along that are even better. But antibiotics are no longer being found with any regularity, and there is worry that that is because there are not many left to be found. All antibiotics have a limited life-span. All will ultimately lose so much of their effectiveness for the most important diseases they treat that they must be replaced. Unless new ones can continue to be found at a considerable rate, a rate at least sufficient to balance the rate at which old ones are being lost, society will one day face a great reckoning. AIDS may multiply by several-fold the rate at which antibiotics need to be found in order to stay ahead of that reckoning. This is a very large problem.

2.3. Transferring new diseases into the species

The third way in which AIDS will kill those who do not have HIV is, in my view, far more important than either of the first two. AIDS will greatly weaken the species immune system, the system that keeps new pathogenic organisms out of our species. Entirely new

diseases will emerge that never would have existed but for AIDS. They will infect not just AIDS patients but the general population. If ever AIDS is eradicated, many (in my view, most) of these new diseases will remain, sickening and killing human beings down the generations, quite possibly for as long as the human race persists. Though bird flu, should it successfully transfer, will probably be a temporary, rather than a permanent, resident of our species, it has the potential to kill a substantial fraction of the human race, and to do so very quickly and very soon. Though there are some other animal diseases that may well have equal or greater potential destructiveness if AIDS ushers them in [8], the opportunity for them to make the species jump has been around for some years now, and they have not yet succeeded (at least not the ones that would show up fast). Bird flu is new, and has just recently made its way into Africa, with its huge populations of the HIV-infected. In my opinion, at least in the short term, it is the greatest danger. In the longer term, other immune-deficiency viruses may be even worse, since they will further weaken the species immune system and allow still more new pathogens into our midst.

The mechanism through which AIDS will lead to species transfer is very clear: As mentioned earlier, the immune system of the individual is a part of the immune system of the species. Individuals with greatly weakened immune systems allow the infection by organisms that cannot survive in normal people; that is, they allow infections to enter the human race that under other circumstances could not do so. At first they may enter only the very most severely immune-compromised AIDS patients, a small subset of the human race. They will not be able to spread from these to the non-AIDS population. But they will in many cases be able to spread to others of the most severely ill AIDS patients.

As they pass from patient to patient, spending more and more time in their new host species, they will begin to adapt to the new environment they find themselves in. After a few patient-to-patient passages among the sickest AIDS victims, they will have adapted well enough to pass to those a little less sick, with immune systems a little less compromised. And as this slightly-more-hostile environment is in turn conquered, they will be able, after a few more passages, to infect AIDS victims at still-earlier stages.

The spectrum of immune system damage among HIV cases forms a *continuum*, stretching from the very sickest all the way to the perfectly normal. There are no gaps to impede the progress of this new pathogen in its evolution toward the ability to infect the human race as a whole. Once it has achieved this ability, it will have passed over this bridge supplied by AIDS, and will have no further need for it. It will go on infecting humanity even if AIDS itself is eradicated. It may continue to do so for as long as the human race survives. So far, in all of human history, we have managed to eradicate only one established disease from our midst (smallpox). Once a disease is established, it becomes extraordinarily difficult to remove.

The sickest AIDS cases provide a stepping-stone for new diseases, reducing the gap between the human race and the disease's normal host. Crossing even that reduced gap may be difficult, but many organisms are accomplishing it, as witnessed by the many infections seen in AIDS patients that are never seen among normal people.

But there have always been individuals with impaired immunity; genetic defects can cause at least as severe an impairment as can AIDS. The difference is in the numbers: the genetic cases are extremely rare, and the unfortunate individuals so afflicted die within the first months or years of life. (This has always been so up until the recent past, when it has been possible to keep such children alive in a "bubble." But the only reason they can survive is that they are never exposed to the pathogens and so do not represent a

stepping-stone for their entry: the missing gap otherwise provided by a healthy immune system is replaced by a gap made of plastic.) In all previous human history there were never more than a handful of such severely immune-compromised children alive in the world at one time. Hardly ever would one such individual pass a novel infection on to another, and almost never would the second child pass it on to a third. Even in cases where parents had several affected children, their survival in premodern times was so short that it is unlikely there would be two severely-immunocompromised children alive at the same time (except in the case of twins), and far less likely still that there would be three.

The weakening in our species immune system represented by these children existed, but only in very small numbers for very short times. The tens of millions of present and future instances of severely compromised immune systems due to AIDS have never before existed, never been approached, not one hundredth as many, not one thousandth as many, not anywhere close to that. It is not merely a quantum change but a gigantic quantum change, amounting to a difference in kind.

Moreover, the rare stepping-stone represented by one of these children was a single stone somewhere in the middle of the gap. The large gap remaining between this child and the rest of the human population had to be crossed in one further leap, in the course of a single infection. In two infections the new pathogen had to be able to move from its former state of adaptation in its previous host all the way to the general population of its new host. It is clear that in the vast majority of cases, the crossing would not have been made.

It is the continuum of subsequent stepping-stones after the first, amounting to a complete bridge of stepping-stones, conducting the new pathogen all the rest of the way into our species, without even any tiny further gaps to impede its progress, that most sharply differentiates the current epidemic of AIDS from the case of the immune-deficient children. It represents an even bigger difference in kind than does the immense increase in numbers.

The pathogens do not have to adapt in the course of a single infection. They have as long as they want, as long as it takes, to slowly, slowly, by degrees, adapt themselves to the general population.

3. Deliberate cross-species transfer

For over 100 years, scientists have been deliberately transferring diseases from one species to another. Most often this has involved the reverse of the transfers we were concerned with above: from humans to animals rather than the other way around, so that human diseases can be more readily studied in animal models.

As a result of this decades-long effort, a great many transfers of human diseases to other animals have been accomplished. Though there still are microbes that have stubbornly refused to infect any other species, despite science's best efforts, methods have been developed that are very frequently successful.

Some of these methods are extremely similar to the method via which AIDS may transfer diseases into our species. Animals with weakened immune systems are used, because they can often be infected when normal individuals cannot. There may be a combination approach: newborn animals, whose immune systems have not yet had a

chance to fully develop, then have their immunity further weakened by means of immune suppressive treatments – e.g., a 25-mg injection of cortisone into a one-day old duckling, followed by another 25 mg four days later (Kuwata, 1964) [9], or a large dose of x-rays to damage the immune system (Maruyama and Dmochowski, 1973, pp. 69-70). Then, if the microbe can be made to successfully infect these weakened individuals, it is passed from them to other weakened individuals for a few times, in order to give the organism a chance to adapt to these easy targets. It is then passed to less-impaired individuals (older or with smaller amounts of the immune-suppressive treatment). Finally, after more passages in successively less-impaired individuals, the microbe may be able to infect normal, adult members of the species.

It frequently happens that the new microbe becomes more pathogenic in the new species as it becomes better adapted and can infect with greater ease (Locher et al., 2003).

Often, the first attempts fail. Therefore, many individuals are used, and several strains of the pathogen are tried, in the hope that one individual may prove susceptible to one of the strains. This, also, is duplicated in the case of AIDS.

The one notable difference is that the deliberate attempts often involve very large doses of the pathogen, far larger than might be encountered naturally, and the exposure is made as intimate as possible, usually via injection, sometimes directly into the most susceptible tissue, such as the brain. There would be no parallel to this in the case of the AIDS transfer, unless a transfusion from an infected AIDS patient (who was presumably not yet showing many symptoms of either AIDS or the new disease) was given to another AIDS patient. This would no doubt be a very rare event; but a lesser version of the same thing would occur whenever non-sterile needles were reused on different AIDS victims. Since many AIDS victims acquire HIV precisely because they are drug addicts who reuse non-sterile needles, in communities of other drug addicts with high incidences of AIDS, this will occur very frequently.

4. Some sample calculations

4.1. The case of those with normal immune systems

In the specific case of bird flu we do not need to concern ourselves with the possibility that huge doses of the virus might be required to produce infection. Healthy, non-AIDS patients are acquiring the infection quite naturally.

Still, it is an extremely rare event. An infected chicken stands only one chance in many thousands of passing its infection to a human being. A human being infected by such a chicken may have either a significantly lesser or significantly greater chance of passing the infection to another human being. The microbe is now at least somewhat human-adapted, and it will therefore almost surely require a smaller dose of it to produce an infection. But we don't know what the relative doses are, nor the means of exposure. Perhaps the first case was infected only because he cut himself while slaughtering sick chickens. Or perhaps, because the virus grows so well in chickens, the sick birds excrete far more virus than the sick people do.

There have been very few cases of human-to-human transmission of bird flu, perhaps on the order of 40 to 60 in all, 7 of which occurred in a single cluster in Indonesia (WHO, 2006a; Normile, 2006; Olsen et al., 2005) [10]. With a total of 556 bird flu cases through 3 June 2011 (WHO, 2011), this means a human being infected by a bird has roughly a 10 percent chance of passing it on. It is clear that an infected person is far more likely to pass his new germ to another human being than is an infected chicken.

Though it is possible with certain animal microbes, as argued two paragraphs above, that transfers might occur from animal to human more readily than those first infected humans can transfer it to other humans (an example would be bubonic plague, easily transferred to humans from fleas but not easily transferred human to human), it will virtually always be the case that those humans who are infected by other humans will be able to pass it on more readily than humans infected by animals. Some degree of adaptation to its new environment will have occurred in the course of this additional infection. And with each further human-to-human passage, the adaptation will increase. If a chicken-infected bird-flu victim averages 1/10 further infection, this is only 10 percent transmissible enough to create a self-sustaining epidemic. But the unlucky 10 percent who are infected, will transmit it on more than 10 percent of the time, potentially much more.

In the cases of deliberate artificial transfers, it may take no more than 6 or 7 successive passages among the weakened creatures before the transfer has been accomplished and the new disease is able to infect even the strong and healthy. It may also take many more passages [11]. But flu is among the most rapidly evolving organisms known. Indeed, bird flu patients treated with Tamiflu have had their virus evolve resistance in as little as four days (de Jong et al., 2005; Le et al., 2005). My guess is that by the time bird flu has passed person-to-person 6 or 7 successive times, the transmission rate will have grown to exceed one per case. Unless promptly stamped out, an epidemic will follow. This is, of course, just a guess, and it certainly could take more passages. But since many of those who are worrying about bird flu jumping to humans seem to think the adaptation will take place in birds and that the first case of a transfer of such a strain to humans will be able to spread to more than one further human, this is in fact a rather conservative estimate.

But there is another sense in which my estimate is not conservative at all. Many experts think a human epidemic would require a change in the bird flu while in birds. Others think it would require recombination between bird flu and an existing human flu (whether in a person or in a pig). I, on the other hand, think the current bird flu is very likely already adequate to start an epidemic, but that many more bird-to-human transfers might well have to occur before the purely chance passing-on through several successive victims serves to produce a human-adapted strain. I believe the current bird flu is already well-enough adapted that the remainder of what is needed can occur through the routine, ordinary, expected adaptation that will surely occur as it passes from human to human, so long as it is able to pass enough times, which might well be as few as 6 or 7.

If we make a few simplifying assumptions, we can easily calculate what the odds are of a single case caught from a bird succeeding in passing itself on through, say, 7 levels of human-to-human passage. Therefore, we can calculate how many such cases caught from birds are required before such a circumstance becomes likely, under these assumptions.

Let us pick 0.1 as the initial transmissibility of those cases caught directly from birds and assume that it increases to 1.0 over 6 equal steps. If transmissibility increases by a constant factor of 1.468 for each step (which is the 6th root of 1/.1), then we will have 0.1 new human cases deriving from each of those infected by birds (the first human-to-human

passage), who will in turn infect 0.1468 cases each (the second passage), who will infect 0.2155 cases each (third), who will infect 0.3164 cases each (fourth), who will infect 0.4644 cases each (fifth), who will infect 0.6818 cases each (sixth), who will infect 1.0 (the seventh human-to-human passage). If there are 1,000,000 cases caught directly from birds, then these will infect 100,000 more, who will infect 14,680 more, who will infect 3164 more, who will infect 1000 more, who will infect 464 more, who will infect 316 more, who will in turn infect 316 more. Thereafter, human-derived cases will cease to fall with each generation of spread, and – unless societal measures are sufficient to counter it – the inevitable further increase in transmissibility with succeeding passages will lead to an epidemic. 1,000,000 cases from birds was about 316 times what we needed. 3165 cases caught from birds would stand a substantial chance of starting an epidemic.

In fact, in order to make the likelihood greater than fifty-fifty, we need to multiply this number by about 3. This is because when the population gets down to 1 infected person whose transmissibility is not much above 1.0, there is a substantial chance the person may infect no one (or that the one or two people he infects may infect no one...), causing the potential epidemic to die at that point. According to May et al. (2001), under reasonable assumptions about the variability of the transmission success from one infected person to the next, the equation for the chance that the potential epidemic will die out (even though the transmission rate is above 1.0) is 1 divided by the transmissibility raised to the *n*th power, where *n* is the number of infected individuals. But this is when the transmissibility is constant. Here it is rising rapidly as the new infection adapts to its new environment, so this equation will overstate the chance of the infection dying out. If the minimum population is set to be 3, instead of 1, then we see that the equation says there is a 50-50 chance of an epidemic if the transmissibility is greater than the cube root of 2. That is 1.26, a value that would likely be surpassed in one more generation, according to the rough case I am describing.

Consequently, instead of 3165 cases, it might take around 10,000 cases of bird flu, as it currently exists, caught by human beings before an epidemic became more likely than not.

It must be emphasized that these numbers are for illustration only, to make clear the principle that is at work, a clash of two opposing forces: a diminishing number of infectees whose infectiousness is growing with each succeeding generation of spread. Assuming the infectiousness will eventually surpass 1.0, then given a large enough initial number of infected individuals, the growing transmissibility will ultimately overcome the diminishing numbers, resulting in an epidemic. But it might take either more or fewer human-to-human passages than the 7 of my example before a strain emerges that could increase its numbers in humans, and the figure I came up with is highly dependent on this number of passages and on the transmissibility of cases infected directly by birds.

The calculation has a lot of terms that can be combined, and when this is done the formula is quite simple [12]. If there are *B* cases caught from birds and these cases infect *Br* more (where *r* is less than 1 or we already have everything needed for an epidemic), and if we increase *r* by a constant factor for each additional human-to-human passage until it reaches 1.0 after *p* passages, then the original *B* cases will fall with each successive passage until a minimum is reached after *p* passages, and thereafter it will begin to rise. This minimum is given by $Br^{p/2}$.

If the minimum number of cases given by this expression does not fall below 3, then there is probably a greater than 50 percent chance for an epidemic. Setting the minimum equal to 3 shows that an epidemic is likely if the number of cases caught from birds, *B*, is at

least equal to $3/r^{p/2}$.

The assumption of a constant factor of increase in transmissibility from passage to passage is probably reasonable. It implies that the rate of improvement, which must ultimately fall to zero as adaptation to humans reaches its maximum, is constant for at least the first *p* generations of spread. The estimated transmissibility for the 1918 flu was approximately 2 to 3 new cases infected by each current case (Mills et al., 2004). If bird flu is capable of ultimately reaching this value, then 1.0 is half or less its ultimate transmissibility, so that we will not yet be nearing saturation, and those limiting effects will not yet be strong. The error introduced by deviations from constancy will probably be small in comparison with errors accruing from uncertainties in *r* and *p*.

We can see from the above equation that increasing *p* by 2, from 7 passages to 9 before transmissibility reaches 1.0, multiplies the number of cases that must be caught from birds by 1/*r*, and when *r* is 0.1, this is a factor of 10. If 5 passages would suffice, then *B* is reduced by a factor of 10. Similarly, reducing *r* to 0.05 increases *B* by a factor of $2^{p/2}$, which amounts to 11.31 when *p* is 7.

Without attempting to justify it, I would say that a reasonable range of values for *p* is 4 to 9. (A *p* of 4 implies a chain involving 5 humans, since one human-to-human passage involves 2 humans.) And I would similarly give 0.05 to 0.15 as about the limits of the reasonable range for *r*, the initial transmissibility when first caught from birds. If these are correct, then a worst case of $p = 4$ and $r = 0.15$ would imply that 133 infections caught from birds might easily spark an epidemic, while a best case of $p = 9$ and $r = 0.05$, would require 2,147,000 infections from birds to present an equal risk. The number given earlier, around 10,000 when *r* is 0.1 and *p* is 7 would be my best guess.

But even if we knew that *r* was exactly 0.1 and *p* was exactly 7 and that the assumption of a constant factor of improvement was correct, chance effects would still play a large role. The epidemic will be started by one particular case that succeeds in passing itself on 7 times. There is a small chance this could be the very first case, and a not negligible chance that it could be among the first few hundred cases. As of 3 June 2011 we had already had 556 cases (WHO, 2011). It apparently has not happened yet, but the Indonesian cluster may have come very close. Eight people in one family were infected, and seven of those are believed to have been infected by a human being. And there was at least one case of human-to-human-to-human passage (Normile, 2006). Since no clear tie to infected poultry has been found for any of these cases, it is possible the very first case also caught it from a person, in which event there was (at least) one further level of human-to-human transmission.

4.2. Considering the effect of AIDS

The above calculations were made without considering the effect of AIDS. However, AIDS may make a very large difference.

There are many opportunistic infections among AIDS patients that just never occur in those with normal immune systems. If a typical, first-passage flu case, caught from a bird, stands even a 5 percent chance of infecting a normal person, it may well infect severely immunosuppressed AIDS patients with relative ease. In a population with many AIDS

patients, the number of primary cases caught from birds needed to spark a human epidemic will likely be far less. It might, for instance, easily reduce the necessary number of passages from 9 to 4 and increase the initial transmissibility from 0.05 to 0.15, and we have just seen that these two changes would reduce the number of cases caught from birds before an epidemic becomes likely from over 2,000,000 cases down to less than 150. And AIDS might well have an even larger effect on both these parameters. I am not speaking of the virus becoming self-sustaining among populations with little AIDS in 4 passages, but that it might well become self-sustaining as quickly as that among populations with many AIDS cases. And once it becomes self-sustaining there, it is only a matter of 5 more passages (which, since it is self-sustaining, now are extremely likely) taking but a few days each, before the maximum hypothesized 9 passages necessary for spread among non-AIDS populations has been achieved.

There are now whole countries in Africa where the HIV-infection rate of the adult population approaches 40 percent, and within these countries there must be some towns and villages where the infection rate is much higher. Of course, most of these HIV-infected individuals have not yet progressed to AIDS, but the presence of many AIDS sufferers even randomly dispersed will substantially reduce the number of cases that must be caught from birds before an epidemic becomes likely, while at the same time quite probably disproportionately contributing to these initial cases caught from birds. The greatest danger, however, occurs when there is clustering of AIDS patients, such as might be found in AIDS wards of hospitals. Here, a mere handful of patients can suffice to form a chain 4 or 9 links long.

4.2.1. Bird flu in AIDS patients

Specifically in the case of bird flu, AIDS may have an additional effect that would apply in very few other diseases, an effect that makes things even worse. Robert Webster, one of the world's foremost flu experts, has pointed out that the current bird flu (like the 1918 flu) triggers a severe overreaction of the immune system. In fatal cases, this is frequently the cause of death, and indeed this is thought by many to be the explanation for why the 1918 flu especially killed the young and healthy and why bird flu is doing the same thing today: It was the young and healthy who had the immune systems that were capable of giving the strongest overreactions.

Well then, Webster argues, AIDS victims, with their weakened immunity, may actually fare better than normal people, when it comes to bird flu. But while the virus may damage AIDS victims less than others, their weakened immune systems will also do less damage to the virus. The flu virus will potentially survive longer in AIDS patients than in normals, thus gaining additional time to adapt to human physiology. This is exactly what Webster sees in immune-compromised cancer patients infected with normal flu: they remain infected and infectious for weeks instead of days (Pease, 2005).

Each time bird flu infects a human and the chain of infection dies out, whatever adaptation was gained is utterly lost, and the next bird flu case must start over from the beginning. If a case in an AIDS patient lasts for weeks, that may be equivalent to four or five or more human-to-human passages, at least in the time the virus spends in a human body. But each transmission event is also a selection event, selecting for the most

transmissible variety, and this part of the adaptation is not so directly advanced by spending additional time within each body. Nonetheless, the more adapted it becomes to growth within an individual human body, the more likely it becomes that even a small amount of the virus breathed in by a contact will be able to set up an infection.

Not only that, but if their infections last longer, they may also pass them on to a larger number of people than the normal cases do. Further, I would worry that their cases may show quite atypical symptoms, including less dramatic symptoms, so that their cases may be harder to spot. Moreover, since AIDS patients frequently have chills and fevers and diarrhea and coughs and frequently die, such occurrences will arouse much less attention than when a young person in the peak of health suddenly sickens and dies. For all these reasons, there is a significant chance that AIDS victims with bird flu will pass the virus on more frequently, not just to other AIDS patients but to members of the general population, and that each flu-infected AIDS case, if the flu lasts longer, represents an opportunity for significant further adaptation to humanity.

5. Examples

I am far from an expert on infectious diseases, and I did not try to find examples of incipient new diseases resulting from immune deficiency, fearing that would cause too much delay in a situation of considerable urgency. Nevertheless, while researching other aspects of this paper, I happened across several possible examples that seem likely enough to be worth mentioning. I have little doubt that there are many more, and probably many better, examples.

5.1. A word about Version 3

Versions 1 and 2 of Section 5 were virtually identical, but there are large changes to Section 5 for Version 3, prompted by my discovery of serious problems in my earlier treatment of the first example, *Clostridium difficile.* I discuss these problems in note [13], but I suggest reading the *C. difficile* section below, first.

I had rushed too much in preparing the earlier account, but once Version 2 was out and the immediate urgency had receded, I felt able to spend much more time learning about *C. difficile* and correcting the former deficiencies. (I had read 24 papers in preparing Versions 1 and 2; I read 103 more while doing the rewrite.) I did not go back and spend additional time on the other examples in this section, but because they were much less ambitious than my original *C. difficile* treatment, I am fairly confident there are no large errors there. By and large they give standard information, which I think is non-controversial.

The *C. difficile* section, below, is considerably longer and more detailed than the other examples that follow. It demands a bit more concentration, but I think it succeeds in making several important and more general points.

During my extra reading, I uncovered two additional likely examples of new human

diseases, either already here or currently in the process of arriving, and so have added these two new examples to Version 3. I also modified the account of *Mycobacterium avium* complex to add an important piece of information I stumbled across in this reading.

5.2. Clostridium difficile

Clostridium difficile (sometimes called C diff) is a bacterium that is very widespread in nature. It is found in soil, water, on surfaces in homes, and in the feces of many sorts of wild and domestic animals, including at least mammals, birds, and reptiles (Al Saif and Brazier, 1996; Riley et al., 1991), quite possibly also insects (Stevenson, 1966), and perhaps more. Of 2580 samples from various locations in South Wales, *C. difficile* was detected in 87.5 percent of those from river water, 46.7 percent of those from lake water, 50 percent of swimming pool samples, 21 percent of soil samples, 20 percent of samples from hospitals, 2.4 percent of raw vegetables, and 2.2 percent of surfaces within private homes. It was even found in one of 18 samples of chlorine-treated tap water (Al Saif and Brazier, 1996).

It forms spores that can remain viable for many months, perhaps even for years (Wilcox, 2003, p. 476). Many have assumed from its widespread distribution that it is a free-living bacterium that sometimes manages opportunistically to infect the colons of animals, but others have pointed to the fact that the spores are so long lived, and to the fact that the environmental findings have largely, if not exclusively, been in or near areas of human or animal habitation (e.g., the 2580 samples mentioned above were all taken in the vicinity of the major city of Cardiff, Wales), and concluded that much or all the *C. difficile* found outside of living animals was due to contamination from their feces.

It is important for my purposes in this section to resolve the question. However, despite a good deal of effort, I was unable to do so. Even a single report of finding it buried in a peat bog (Martin et al., 1982) does not help, because burrowing animals, including earthworms, nematodes, and insects, could have carried spores down from the surface on their skins, or, indeed, provided homes for the bacteria within their alimentary canals.

Spores of *C. difficile* can also be found floating in the air. In areas near patients ill from the infection, their concentration may reach more than 400 per cubic meter (Roberts et al., 2008). Such spores would be breathed in, potentially several thousand per day, where many of them would be swept by the cilia of the respiratory tract up into the throat and swallowed.

It is very clear that it is not possible to avoid coming into contact with and ingesting this bacterium or its spores, and it is likely that this will occur with great frequency. The bacterium is capable of causing serious and occasionally fatal consequences, including most often diarrhea, sometimes difficult or impossible to treat, and less frequently, colitis, peritonitis, or worse. A peculiar and very bad form of colitis, called pseudomembranous colitis, is almost always due to infection with this organism.

If the organism is so widespread and can cause such serious consequences, why are we not all made sick by it? Two factors, two aspects of our immune system, protect us. Stomach acid kills the bacterial cells. This is helpful but only mildly so, because the spores are not killed. Far more significant are the friendly bacteria and other friendly flora living

within our intestines. When we have a well-balanced and flourishing set of friendly flora, *C. difficile* is usually not able to survive at all, or only temporarily, and only in such low numbers that we are not even aware of it (Wilson, 1993).

In recent decades two medical developments have caused serious impairments to these two branches of our immune system. Powerful drugs to fight ulcers drastically reduce stomach acid, thus allowing more bacteria to reach the colon. This produces at most a relatively minor effect, which some researchers have suggested does not even exist (Jump et al., 2007). But then antibiotics, which so helpfully kill so many terrible pathogens, enter the picture to also kill the friendly flora we need to keep the *C. difficile* in check. The great importance of the role played by antibiotics is undisputed.

Pseudomembranous colitis was first diagnosed in 1893, but was an extremely rare condition before penicillin came into use, beginning in 1943. Shortly thereafter, an increasing incidence of pseudomembranous colitis began to be noticed. It was quickly linked to antibiotic use, but not until the late 1970s was the true cause found to be *C. difficile* (Bartlett, 1994).

Until recent years, symptomatic *C. difficile* infections were confined almost entirely to debilitated residents of hospitals and old-age homes who had been treated with antibiotics. Because *C. difficile* is so much more resistant to most antibiotics than are the friendly bacteria, such treatment provides an ideal "fertilizer" to turn an asymptomatic, probably temporary, minor infestation of *C. difficile* into a raging infection. And since reconstitution of the normal bowel flora may take some time to occur (and may be aborted by further antibiotic treatments), during the time when the friendly flora are deficient even uninfected patients are ideal targets for the *C. difficile* that infects other debilitated patients in the hospital or nursing home, whose diarrhea contaminates their surroundings and the hands of attendants with *C. difficile*, whose spores are so long-lasting and additionally are resistant to many cleansers and antiseptics, including especially the alcohol-based products that have become quite popular but which do not kill *C. difficile* spores (Sunenshine and McDonald, 2006; Jump et al., 2007, pp. 2883-2884).

For the past decade or so, however, increasing numbers of severe cases have been turning up within the community at large, among young, previously healthy individuals who have not had any recent antibiotic exposure. About 9 percent of all cases acquired in the community (i.e., outside of hospitals or old-age homes) in Connecticut, USA, in 2006 had no recent antibiotic exposure, advanced age, debilitation, hospitalization, or other known predisposing factors (Centers for Disease Control and Prevention, 2008; Centers for Disease Control and Prevention, 2005). Such cases used to be very rare.

The simplest, and in my view the most probable, explanation for this recent worsening of *C. difficile* is that it was not a human infection before the first antibiotics produced large numbers of friendly-flora-deficient humans, with modern hospitals and nursing homes concentrating them into assemblages where the infection could pass easily from one highly-susceptible individual to the next, and with a continuous influx of new patients to infect.

There are, however, two other main possibilities. Perhaps *C. difficile* was a human infection all along, extending back many thousands of years, and something about the current, changed environment, presumably directly or indirectly connected with antibiotics, has caused it over the last decade or so to begin to worsen with great speed.

But it also could have crossed over into our species somewhere in between these two

extremes, namely a few hundred years ago, through a different susceptible group. Human infants (and in general the infants of mammals and birds, at least, and probably other creatures as well) are born with no protective flora in their intestines. Indeed, there are no flora at all: their intestines are sterile at birth (Hall and O'Toole, 1935; Wilson, 1993). Very rapidly, within hours, the first bacteria begin to colonize this inviting target, but before a viable set of friendly flora becomes established the infants are highly susceptible to infection with *C. difficile*. Studies have found infection rates in human infants as high as 50 percent, and sometimes higher (Wilson, 1993; Wilcox, 2003). *C. difficile* was in fact first discovered in 1935, several years before the first antibiotics, as a common inhabitant of the colons of newborns (Hall and O'Toole, 1935). For unknown reasons human infants are generally immune to the toxins produced by *C. difficile*, and though they may have high levels of the organism in their stools, it is unusual for them to show any symptoms at all.

Within days or a few weeks, as the friendly flora begin to take over, *C. difficile* levels begin to fall, usually disappearing within a few months, and nearly always by the age of two or three (Fekety et al., 1981; Wilcox, 2003). A newborn infant is an ideal environment for *C. difficile*, and if this pathogen has been with us from the beginning, it likely entered through this route. But during the short period during which the infant is infected, and the often very short period during which it is infected with large numbers of organisms and therefore highly infectious, it must find another newborn, or nearly newborn, infant to infect. Before the advent of hospitals with maternity wards, a few hundred years ago, it seems doubtful that there were sufficient concentrations of newborns to provide the means for the infection to continue. The first orphanages originated many centuries earlier, but they likely contained much lower concentrations of newborns. Perhaps a social historian could provide more concrete data, but my cursory thinking leaves me doubting anything before the first sizable maternity wards could have sufficed, particularly since the *C. difficile* rate among infants back then would likely have been much less. After all, home-born babies would not have been exposed to the contagious environment of the maternity ward, full of long-lived spores, infected babies, and attendants with contaminated hands.

Whenever it entered, it is very clear that *C. difficile* is a human infection today. It is very clear that it is not like Ebola (but *far* more common), entering humanity from a non-human source and perhaps managing to survive for a few generations of person-to-person spread, but always ultimately dying out. We know this through the rapid adaptation that is occurring among the worst strains of *C. difficile*. The so called "super" strain, PCR ribotype 027, has gone from being a rare, ordinary strain occurring in only 14 out of 6000 samples taken before 2001 (Warny et al., 2005), to now being the cause of large epidemics, in both North America and Europe, where it may sometimes constitute more than 80 percent of all strains (Birgand et al., 2010). In Canada, strain 027 went from being undetected in 2000 to making up 75.2 percent of all PCR-ribotyped strains in 2003 (Stabler et al., 2009). The death rate is substantially higher, and the *C. difficile* is resistant to many more antibiotics. An early sample of this strain, from 2002, was susceptible to erythromycin, ciprofloxacin, and moxifloxacin, while samples from 10 hospitals and a nursing home in various parts of the Netherlands, just a few years later, were resistant to all three. In just a few years, this strain has become able to withstand more than 1024 times as much erythromycin, more than 168 times as much ciprofloxacin, and more than 256 times as much moxifloxacin (Goorhuis et al., 2007).

And there are other strains that are also now clearly human, as shown by their rapid

spread, adaptation, and acquisition of antibiotic resistance.

Exactly when *C. difficile* became a human infection is a matter of great importance. When strains enter from the environment only to die out after passage through a relatively small number of human beings, then whatever adaptation was accomplished during this brief sojourn is lost. The next human infection must start over from the beginning. But when generation after generation of human infection persists, then each generation can build on the adaptation achieved by its predecessors. As it adapts, it becomes better able to infect human beings, better able to cope with their defenses, better able to persist despite some of the normal intestinal flora, perhaps ultimately able to persist and cause disease even in the presence of all of the normal intestinal flora, even in previously healthy people with no hospital or antibiotic exposure. An opportunistic infection of a small part of the human race with a damaged immune system will have become a disease affecting the whole population.

If this is an age-old infection, then it is very likely that it has already adapted to our species about as well as it is capable of doing and should not get much worse in the future. It will become harder to treat as it gains more resistance to more antibiotics, and theoretically it could become a little worse if adaptation to antibiotics causes it to produce more diarrhea (see note [13]). But it should not ever attain the ability to infect new populations that it could not infect in the past, except for those populations we create for it with our antibiotics. It should not ever become able to infect normal people with normal intestinal flora, except as an occasional, fluke event, far below the threshold of efficiency that would permit it to survive in such a population.

On the other hand, if human *C. difficile* strains only came about after the first antibiotics, this was a recent enough event that it has likely accomplished but a small part of the adaptation it is ultimately capable of. We will likely see considerable worsening of these infections over the coming decades and centuries: much higher infection rates will occur among all population sectors, with the traditional risk groups hardest hit but with many more and worse infections among those not formerly at risk.

And if it has been a human infection since the first maternity hospitals, it will have already accomplished much more of its ultimate adaptation, but will likely have a considerable distance still to go.

What evidence can we provide for the length of time *C. difficile* has been a human infection? My best guess is that it is a new infection which adapted to humans only after the introduction of antibiotics, but the evidence is not sufficient to draw any very firm conclusion. The case for this recent origin rests on two lines of evidence.

The first is a *lack* of evidence for an early origin. If *C. difficile* in fact became a human infection thousands of years ago, that would mean that for many human cases today, there would exist an unbroken chain reaching back thousands of years of other human beings who had passed *C. difficile* on and on and on for probably tens of thousands of human-to-human passages of infection. This evolution of the human strains, thousands of years separated from strains that had been evolving in other animals or within soil, water, or other niches in the environment outside of animals, could hardly have failed to produce large differences in the human strains compared to every other. It would hardly be possible for researchers to have studied this organism for decades and failed to notice these differences.

Several studies have attempted to plot genetic relationships among *C. difficile* strains

taken from humans, animals, and the environment (Stabler et al., 2006; Lemee et al, 2004; Scaria et al., 2010). But except for those aforementioned strains that are clearly now human strains, and are causing the large epidemics, there doesn't seem to be any species specificity. The same strains occur in multiple animals. And while one might say perhaps they are not *quite* the same strains but our techniques are not yet sophisticated enough to tell the difference, this argument is very implausible. The thousands of years of separation between strains specific for one species versus another should have resulted in large differences that would have been obvious even to the early researchers.

This apparent lack of species specificity would lead one to think that the natural home of *C. difficile* is the external environment, but in fact few animals other than pets and farm animals have been tested. These animals have all been heavily exposed to antibiotics, so that even strains specific for other animals might well be able to infect them. Therefore, many wild animals will need to be tested before putting much faith in this conclusion. Nevertheless, the fact that no human-specific strain that obviously branched off from the others long ago has been found, does lend a good deal of weight to the possibility that there were no human strains before the antibiotic era, even if perhaps there were strains specific for certain wild animals.

Likewise there are a great *many* strains infecting human beings – depending on how they are characterized, perhaps 100 or more (Kuijper et al., 2009; Lemee et al, 2004). Yet for organisms that have long ago adapted to our species, there are generally just one or a few varieties. All the other contenders have been squeezed out through the intense competition with these very best few. And while a sudden expansion of the environment caused by antibiotics might allow room for non-human-adapted opportunists to gain a brief foothold, they would be so inferior to strains that had been living in the human colon for thousands of years that they would be rapidly displaced. Their inferiority as competitors would be as obvious as the other differences that had accumulated over thousands of years of separation.

The other line of evidence is a positive one, but enough data are not yet in to reach a firm conclusion. This evidence is dependent more on time than on research, and as time passes, this evidence will become stronger, perhaps a great deal stronger, if in fact *C. difficile* is a new human disease. The evidence is just the considerable increase in cases and worsening of cases that I mentioned earlier. A two- or three-fold increase in numbers of infections and in the percentage of deaths, such as we have seen (Warny et al., 2005; DuPont et al., 2008), might be due to some other factor, or combination of factors. For instance, some have wondered whether the increase is not, at least in part, due to our sudden greater interest, leading to more and better testing of possible cases, with fewer missed cases. At the present time, such wondering is legitimate. But if in another ten or twenty years the incidence among those previously not at risk has increased another ten or twenty times, it will be hard to argue for any other cause than that a new pathogen has begun adapting to our species.

It might be impossible to decide between the case of *C. difficile* having first entered after the introduction of antibiotics or after the introduction of maternity hospitals. The time between the two events is probably sufficient, at least if *C. difficile* continues to *rapidly* worsen, to pin it to a more recent date than the introduction of maternity hospitals. But even if the transfer became possible after the first of the hospitals, that does not mean that it happened immediately. If in fact the transfer occurred only a decade or two before the first

antibiotics, then there is likely never going to be any way to decide.

At the very beginning of Version 1 of this piece I listed friendly flora as part of my extended definition of the immune system, yet it was not until the additional reading I did in connection with the rewrite of this section that I began to appreciate just how vital a part it was. For the damage antibiotics are doing to this branch of the immune system puts us at risk for many new human intestinal diseases (and a lesser number of non-intestinal diseases).

The friendly flora consist of hundreds, perhaps thousands, of species of micro-organisms (mainly bacteria). These organisms are highly adapted to the human colon and to each other. Indeed, though there are many mouth bacteria which have counterparts in the colon belonging to the same genus, there is almost no overlap in actual species, each being so well adapted to its own particular preferred environment (Walk and Young, 2008; Wilson, 1993).

The friendly flora are symbionts: in return for the sheltered habitat and food supply our intestines give to them, they provide us with vital services. They help to digest our food; they manufacture certain vitamins and other useful substances; they produce compounds that kill pathogenic bacteria; they modulate our immune systems in several helpful ways. Some very insightful thinkers have considered them so complex, so specialized, and so highly co-evolved with the rest of our bodies that they should be called a virtual organ within an organ (Dobrogosz et al., 2010).

There are at least 10 times as many friendly bacterial cells within our colons as there are human cells within the rest of our bodies. These bacteria fill their environment chock full. And because they are so well adapted to our colons and to each other, there is little opportunity for a new invader who has never seen a human colon before to get a foothold. An invader needs to fasten to the wall of the intestine in order not to be swept out with the next bowel movement, yet virtually all available spots are already taken. It needs a food supply, yet its abler competitors secure this nearly all for themselves. In addition, they produce chemicals which poison many bacteria that are not already acclimated to them (Wilson, 1993; Dobrogosz et al., 2010). Thus, perhaps the most important of all the services performed by our friendly flora is to keep those organisms which are not coadapted to this ecosystem *out.*

We have seen how well this works with *C. difficile.* A normal person probably swallows a few *C. difficile* spores almost every day. A worker in a hospital gastrointestinal ward likely swallows hundreds, and perhaps thousands, of spores every day in which there are a few *C. difficile* patients on the ward. (Even the most scrupulous personal cleanliness cannot protect against spores breathed in and subsequently swallowed.) A new mother will be heavily exposed to *C. difficile* whenever she changes her infant's diapers, in the many cases when the infant is asymptomatically infected (Wilcox et al., 2008). And yet a normal person, with a normal complement of friendly flora, is not at risk from all this exposure. The risk comes only when the friendly flora is damaged.

A most striking example of this protection occurs in hamsters. One colony-forming unit (cfu) of a microbe is the amount that when spread onto culture medium will result in the growth of one colony. When 20 normal hamsters were given 75,000 to 2,000,000 cfu of *C. difficile*, they showed no symptoms; and when killed after 30 days' observation, *C. difficile* was detected in only 1. Evidently, normal hamsters are highly resistant to *C. difficile.* But when given an antibiotic to kill their friendly flora, hamsters become extraordinarily

susceptible. They are very likely to pick up the infection from the environment, and it nearly always proves fatal for them. Animals put into strict isolation long enough for their friendly flora to recover remain well, but it takes only 1 cfu of *C. difficile* deliberately fed to such an animal to produce a fatal infection. A normal hamster is not even made sick by 2 million times the dose that kills an antibiotic-treated animal. This is the protection from *C. difficile* that a hamster's friendly flora provides (Larson et al., 1980; Larson et al., 1978).

(Clearly humans are not as susceptible as hamsters, since even debilitated humans with much higher exposures to antibiotics are fairly unlikely to get *C. difficile* at all, and will in most cases survive it when they do get sick, even if they do not receive any treatment.)

Germ-free mammals, delivered by caesarian section into a perfectly sterile isolator, so that their colons remain sterile so long as the isolation is maintained, have been used to study the importance of the friendly flora in keeping pathogenic bacteria out. Three to five *Salmonella enteritidis* bacteria are enough to kill 50 percent of germ-free mice. But it requires a million times more such bacteria to kill 50 percent of normal mice (Collins and Carter, 1978, Table 1).

These are no doubt extreme examples, but how many others must there be where a 10- or 100- or 1000-fold effect exists? Even a two-fold effect would be significant in the case of pathogens that are occasionally able to infect humans but are unable to adapt to our species because they pass themselves on to too few secondary cases. Those that can pass at least half an infectious dose to the requisite number of secondaries would now have an opportunity to adapt.

And once adapted to our intestinal systems, they are one very large step closer to being able to spread to other parts of our bodies and adapt to those. They have gained a foothold in the human body, which they never had before. They now have decades, centuries, or millennia to expand that foothold elsewhere.

Interestingly, I earlier described antibiotics as an important part of my extended definition of the immune system. But at the same time they may well constitute an even more important part of the anti-immune system. They seriously damage the normal intestinal flora, and we now see what a key role this plays in our immunity. They provide another gateway through which brand-new organisms may invade and adapt to our species.

The worst *C. difficile* strains are now resistant to many antibiotics, and we might think we could date the first human strains to (or before) the first acquisition of antibiotic resistance. After all, strains found in nature would not have been exposed to antibiotics and thus could not have developed resistance. How could the first human strains have entered *after* their acquisition of resistance?

But this reasoning is not correct. In fact, there is an important class of non-human microbes that receives considerable exposure to antibiotics: those in our pets and domestic animals. Indeed, farm animals may receive extremely high exposures. One can imagine that *C. difficile* infecting pigs, say, developed resistance to multiple antibiotics through their heavy exposure. (Perhaps there was already a pig-specific strain; or perhaps the antibiotics created it.) These resistant microbes were therefore better equipped than their non-resistant brethren to infect friendly-flora-deficient human beings. We had several fewer weapons to combat them (the several antibiotics they were resistant to), and they had an improved substrate, a nice, pristine intestine without all those friendly flora to stop them. It was a substrate all their non-resistant relatives would have had trouble capitalizing on, what with less flora but more antibiotics.

There is, in fact, evidence that this is how another prime candidate for a new human strain of *C. difficile* arrived. The PCR ribotype 078 strain is also causing widespread outbreaks of severe disease, and it is a common strain in farm animals (Bouvet and Popoff, 2008). It has, in fact, been found so frequently in meat samples that there may still be some question as to whether it is truly a human strain or merely a pathogen we are catching from our food. In other words, there may still be some question as to whether it would persist, or die out of its own accord, if all infections from tainted food were halted. Either way, it is very likely in my view that 078 has been infecting humans as a result of heavy antibiotic use in farm animals, and if it is not yet an example of a truly-human disease that entered through this novel weakness, that it will probably become one shortly. (But see note [13] for alternatives.)

Not only are existing animal diseases made antibiotic resistant, but new diseases may enter the animals via their lack of friendly flora. Both old and new animal diseases may then make their way into human beings (especially if we, too, are friendly flora deficient).

It appears, therefore, that antibiotics can damage the human species immune system even when they are used in animals. Even if (as seems likely) the original human *C. difficile* strains transferred without the aid of antibiotic-treated animals, it is clear that antibiotic use in our domestic animals may at some future point infect us with other new organisms (including more, perhaps worse, strains of *C. difficile*). Indeed, if antibiotic use ever permits an organism from the environment that previously was unable to live within any animal species to adapt to the intestines of one animal, it will be far closer to adapting to every other animal. It will be a rather small step from a domestic animal to us, with our antibiotic-treated millions. And if it ever manages to adapt well enough to survive when there is a normal complement of friendly flora, it may thereby gain the ability to infect many other animals, without further need for antibiotic assistance, particularly since the friendly-flora-deficient intestines of infant animals will function as a stepping-stone.

AIDS plays mainly an indirect role in this example. Though AIDS cases appear somewhat more susceptible to *C. difficile*, the difference is not great, and their chief contribution comes about because they are so much more likely than normal people to be heavily treated with antibiotics that make them friendly-flora deficient. My best guess is that the first human *C. difficile* strains entered with the help of antibiotics before the AIDS epidemic began, but that new strains will continue to arise, and that AIDS cases will marginally increase their number.

In general, the many different and new assaults on our species immune system, such as will be discussed later, work in tandem. In the case of *C. difficile*, and in the case of other new (present and future) intestinal diseases, it is likely that antibiotics will be the major player; however, if some of the new diseases later expand their territory to include other parts of the body, AIDS may well play the largest role in this next step.

5.3. Clostridium perfringens and Staphylococcus aureus

While doing my additional research into *C. difficile*, I ran across two similar examples: The ubiquitous microbe *Clostridium perfringens*, which lives in the outside environment, in soil, in decaying plant and animal matter, and also, innocuously, inside the intestinal tract

of animals, can increase its numbers a thousand fold and cause severe, persistent diarrhea which can be mistaken for *Clostridium difficile* diarrhea when it encounters a friendly-flora-deficient intestine (Modi and Wilcox, 2001; Collie and McClane, 1998; Larson and Borriello, 1988; Samuel et al., 1991). It is clear that *C. perfringens* has been a normal resident of the human intestine since time immemorial. But it is not clear whether it is a human-adapted organism because it is not clear whether humans get these bacteria from other humans or from the environment. It may, in other words, be a great generalist which can live in many different environments, and has never specifically adapted to us through repeated person-to-person passage. The large majority of strains produce no enterotoxin and are harmless, normal residents of our intestines. Some toxin-producing strains are among the most frequent causes of food poisoning (generally lasting less than 24 hours and not mistakable for *C. difficile*). But it has been discovered that the strains of *C. perfringens* isolated from patients with antibiotic-associated diarrhea differ in the location of their enterotoxin gene from the less-serious strains that cause food poisoning. Three-quarters or more of all the food poisoning strains have their enterotoxin gene located on a chromosome, while virtually all the antibiotic-associated strains have the gene located not on a chromosome but on a plasmid (Collie and McClane, 1998; Sparks et al., 2001; Li et al., 2010; Asha et. al, 2006; Wen et al., 2003). There have been probable cases of patient-to-patient spread of these plasmid-located strains. There is therefore, also, the possibility these particular strains, with their different toxin gene arrangement, are new and just beginning to adapt to our species, now that antibiotics have greatly facilitated their human-to-human spread, even if the enterotoxin-negative normal residents of our intestines have been human-adapted strains all along.

Increasing resistance to antibiotics, whether of the innocuous strains or the virulent ones, would indicate significant human-to-human passage, which would likely lead to human-adapted strains, unless they were already human-adapted before the arrival of antibiotics.

The other example is *Staphylococcus aureus*, which is a normal and usually harmless inhabitant of human skin and nasal tissues, but which does not normally (or happily) live within the human body. But it, too, can sometimes cause *C. difficile*-like symptoms in antibiotic-treated and friendly-flora-deficient human beings (Gravet et al., 1999; Asha et al., 2006). And there is at least preliminary evidence that in a hospital setting it can spread from one antibiotic-treated patient to the next. If it should successfully adapt to this niche, and expand its beachhead to wider niches, with less-deficient intestinal flora, this could be a very serious matter indeed, particularly since 97 percent of the 47 cases found by Gravet et al. (1999) were of the dreaded MRSA strain of *S. aureus*, already difficult to cure because of multiple antibiotic resistances, and which would become more difficult to cure as it gained both new antibiotic resistances and gained a more secure foothold in its new surroundings, as it improved its adaptation. For 10 of these 47 cases, the *S. aureus* spread into the bloodstream, and 15 of the 47 died.

5.4. Penicillium marneffei

The fourth suggestive example is a fungus, *Penicillium marneffei*, related to the

common mold that produces penicillin. It was discovered in Vietnam in 1956. It lives only in southern, mainly southeastern, Asia. Though other *Penicillium* molds almost never cause human infections, and though this one very seldom does in those with normal immune systems, it has become a very frequent pathogen of those whose immunity is seriously impaired. In Southeast Asia it is the third most common opportunistic infection found in AIDS patients, occurring in 20 percent of AIDS patients in northern Thailand and 10 percent in Hong Kong. It infects lungs, liver, spleen, kidneys, lymph nodes, bones, other internal organs, and the blood. It responds fairly well to antifungal medications, but if left untreated it is nearly always fatal, at least in immunocompromised individuals.

Aside from human beings, the only animals in which this fungus has ever been found are several species of bamboo rat. However, contact with rats does not seem to be the mode whereby humans acquire the infection. Nor does contact with infected AIDS patients. Working around the soil does seem to predispose to infection. This fact, together with the fact that despite its high frequency in Southeast Asia, it does not so far seem to be spreading to AIDS patients in other parts of the world, and the fact that most pathogenic fungi are caught from the environment rather than another infected person, makes it seem likely that this fungus is not currently passing person-to-person with any regularity. If it cannot spread from AIDS patient to AIDS patient, then it cannot improve its adaptation to our species.

On the other hand, it is the only *Penicillium* mold that exists in two different forms. In cool conditions in tissue culture, it grows as a mold. But when grown at 37 C (98.6 F), it changes into a yeast. It is this fact that enables it to become a human pathogen. And because this transition occurs so close to the typical body temperature of mammals (I don't know the body temperature of bamboo rats), it is reasonable to suspect that it is already adapted to the rats. A very high percentage of bamboo rats are infected (usually asymptomatically), and if it is determined that they pass it on to other bamboo rats, I would expect the fungus to have the potential to colonize human beings in the same way. The rats could be catching it from the soil, rather than each other; but the only soil in which the fungus has been detected is soil from within rat burrows (and then only very rarely). Perhaps it is caught from a still-unidentified plant, or some other reservoir in the environment, but extensive searching has so far failed to uncover such a reservoir (Vanittanakom et al., 2006; Supparatpinyo et al., 1994; Chakrabarti and Shivaprakash, 2005; Randhawa, 2000; Restrepo et al., 2000; HKU-Pasteur Research Centre, 2002).

The pathogen has been in AIDS patients for less than 30 years, and for much of that time the number of AIDS patients in Asia was small. Fungi do not adapt as fast as viruses. It will likely take more successive human-to-human passages to produce a human fungal strain than would be true for a virus. These passages may currently be happening very seldom. If so, it may take a very long time to produce a human-adapted strain. Or it may never happen at all. But if the illness begins spreading to AIDS patients in parts of the world far from Southeast Asia, then these passages are occurring, and the likelihood of a strain that can infect normal human beings will greatly increase.

Reading about *Penicillium marneffei* led me to descriptions of several other fungi that may also have the potential to colonize our species (Walsh and Groll, 1999), especially skin fungi, such as *Microsporum* and *Trichophyton* species, which can be spread from person-to-person via contact. More speculatively, some of the fungi that are acquired through inhalation and cause pneumonia with coughing, such as *Pseudallescheria boydii* may also be potential colonizers. There is more to spreading through the air than just acquiring

infection through inhalation which leads to coughing (suppose only spores can lead to infection, and suppose few or no spores are produced in the human body, or few or none are coughed out). But this is enough to prompt a search for cases of airborne person-to-person spread, and to remain alert for the occurrence of such cases in the future, if none are known today.

I include here a brief comment on *Pneumocystis jirovecii* (which used to be called *Pneumocystis carinii*). There is good evidence that this fungal infection, one of the most common and troubling opportunistic infections in AIDS patients, passes person-to-person and that strains from one species of mammal cannot infect dissimilar species. Therefore, it seems almost certain that it has been adapting to mammals, presumably including human beings, since time immemorial. AIDS cannot help it gain entry into our species because it was already here long before AIDS. Thanks to AIDS, it is rapidly gaining resistance to the drugs used to treat it, and this will make it more of a problem for AIDS patients and others with serious immune problems. But the infections that it produces in non-immunocompromised people will not get worse as a result. The great majority of normal human beings becomes infected by this microbe, nearly always in infancy or soon after, but the infection is very mild and antibiotics are almost never needed to treat it (Dei-Cas, 2000; Chakrabarti and Shivaprakash, 2005).

There remains, however, the danger that AIDS might allow one of the strains that infect other mammals to become a human pathogen. Here, we can hope that our own strain, which has had thousands of years to adapt to our species, will suffice to keep all foreign strains from gaining a foothold. Should one of them gain a foothold, we can still hope that our immune system, which handles our own strain of *Pneumocystis* quite well, will be similarly successful with the new one. However, the example of bird flu, or of the herpes B virus of macaque monkeys (National Research Council, 2003, pp. 23-28), which is closely related to our own cold-sore virus and which produces similar innocuous symptoms when it infects macaque monkeys, but which in us attacks the brain, with fatal results in more than 80 percent of untreated cases, shows that this is not always so.

5.5. Rhodococcus equi

The fifth example is a bacterium, *Rhodococcus equi.* It is one of the most important causes of sickness in horses less than 6 months old, usually attacking the lungs. Before the development of combination erythromycin-rifampin therapy, it was 80 percent fatal. Even with the therapy, it is fatal in about 12 percent of cases. It has now begun infecting AIDS patients. In at least one instance, two AIDS patients acquired the infection after being housed in the same hospital room with other AIDS patients who were infected with *R. equi* (Arlotti et al., 1996). The causative organism is a soil bacterium (Giguère, 2000).

5.6. Multidrug-resistant tuberculosis

The sixth example is a variant of one of the most common human infections, one we

have already discussed earlier. Multidrug-resistant tuberculosis is unlike ordinary TB in that the great majority – more than 90 percent in several studies – of those infected are HIV-positive, and most of these are AIDS cases (Centers for Disease Control and Prevention, 1991; Centers for Disease Control and Prevention, 1992). There are two possible reasons, and I suspect they both play a role. As mentioned previously, AIDS patients with TB are far more likely to breed the multidrug-resistant type, since their cases are far more likely to fail to be cured with standard therapy, because their immune systems provide much less assistance. Second, it may be that the various mutations that the TB organism was forced to undergo in order to survive attack by the therapeutic drugs left it weakened and significantly less able to infect people with normal immune systems. This is to be expected, since mutations are nearly always deleterious; and while these particular mutations were selected to help the organism cope with the antibiotics it was faced with, they very probably weakened it in other ways at the same time. Perhaps without AIDS patients and others with compromised immune systems to keep them circulating, the multidrug-resistant TB varieties would simply die out. Indeed, in the one study I found which had a much lower level of HIV-infected people among the multidrug-resistant TB cases they studied (15 percent), the 102 cases they examined spread it to only around 10 percent as many people as would be necessary to keep the multidrug-resistant cases from dying out (Nitta et al., 2002).

Therefore, we can think of multidrug-resistant strains of TB as opportunistic infections, which, through the stepping-stone of AIDS patients, may become much better able to infect the population at large as time passes. Since, in fact, each instance of the development of a multidrug-resistant strain is a separate evolutionary event, and there are already a great many such strains, and what may be true for one of them may not be true for another, I think it is extremely likely that there are at least certain multidrug-resistant TB strains that fall into this category: able to do quite well within the AIDS population but unable to survive without it, but which will gain that ability with further practice. To the extent that there are other strains that could indeed survive without the help of AIDS patients right now, one then needs to ask the question: How many of them started out with this ability, and how many others have gained it only after several passages through AIDS or other immunocompromised patients? In any event, one expects the weakening due to the resistance mutations to grow less with passing time, as the new organisms adapt better and better (Rokyta et al., 2002), so that these strains will likely become progressively worse the longer they manage to inhabit our species.

Before AIDS came along (and after smallpox was eliminated), TB was the worst infectious disease on the planet, in terms of number of deaths, and this was so despite the fact that we had drugs which were really rather effective. Thanks to AIDS, there may come a time in the not-so-distant future when populations that are already unprecedentedly crowded are forced to deal with TB without any very effective treatments.

5.7. Other mycobacteria

The final example, which is not actually due to me but comes from an important paper by Robin Weiss (2001a, which also lists several other candidates), involves bacteria which are relatives of tuberculosis, namely, the *Mycobacterium avium* complex and other

mycobacteria. These bacteria seldom infect anyone who is otherwise healthy, but occasionally manage to infect someone with an intact immune system who has lung problems. When such infection occurs, it is very hard to cure, much harder than ordinary tuberculosis, because these organisms are naturally resistant to several of the drugs used to treat ordinary tuberculosis – i.e., they do not have to acquire resistance through treatment failures, but are resistant from the start (Cumberworth and Robinson, 1995).

But while these bacteria only rarely affect members of the general population, they are a very common cause of illness among the immune deficient, having been found in up to 50 percent of AIDS victims at autopsy (Biet et al., 2005; Cumberworth and Robinson, 1995). Perhaps with the assistance of AIDS, one or more of them will manage to make the jump into the general population. Should this occur, it could be a very serious development.

It is not clear how close the several *Mycobacterium avium* complex bacteria (often called MAC) may be to becoming human infections. They are ubiquitous in nature, living in soil, water, animals, and, it would seem, practically everywhere else, including a substantial fraction of municipal water supplies. Infections are in general acquired from the environment. Only a handful of cases of possible person-to-person spread are known, and I was not able to find a single one that was definite. Since strains of MAC can spread in chickens and other animals, I strongly suspect that occasional instances of person-to-person spread occur, but they are difficult to demonstrate given the huge amount of exposure from other sources. Given that MAC is among the commonest bacteria implicated in AIDS victims with diarrhea (Sanchez et al., 2005), it would seem quite incredible if it could not pass from the penis (or condom) of a man having anal sex with two people, one of whom has intestinal MAC and the other of whom is an AIDS patient. (To think that such a large inoculum transferred into a medium in which MAC can thrive would not frequently result in transfer of infection does seem to me quite incredible; however, I strongly suspect normal anal sex would also suffice to transfer it, though less frequently.)

The ordinary human immune system has a very high resistance to MAC infection. Biet et al. (2005, p. 424) estimate the average person is exposed to 50-500 MAC bacteria every day, yet almost nobody becomes infected with it. This is not as reassuring as it first appears. In nearly all cases of human infection, the microbe is attacking its first, and last, human. How well the ordinary human immune system would do against a strain that was now a human infection, and had already passed human-to-human 10 or 100 or 1000 times, is not at all clear. Our bodies are very good at dealing with non-human, completely unadapted, MAC. They will have a harder time once it has had a chance to adapt.

An experiment will illustrate just how stunningly microbes can adapt to new environments: When researchers transferred a particular virus that infects bacteria from its usual *E. coli* host to a different bacterium (*Salmonella typhimurium*) and increased its growth temperature by about 6 degrees C, at first its reproduction was so diminished that the growth rate was negative. But it soon improved its adaptation enough not merely to maintain itself but to rapidly grow in its new environment. After only 10 days, instead of decreasing by a factor of 3.17 every 20 minutes (which is one generation time of the virus) it was increasing by a factor of 18.0 (Wichman et al., 1999). The authors express it per hour rather than per generation, and their impressive figure of an 18,000-fold improvement in the per hour growth after only 10 days of adaptation has been cited by others. But in fact that figure contains a decimal point mistake: the researchers found that the virus went from -5 doublings per hour (a 32-fold decrease) to 12.5 doublings (5800-fold increase), for a difference of 17.5 doublings per hour, and that is an improvement of 185,000-fold!

The salmonella bacteria may have done fine against the virus when it was adapted to *E. coli* but did not fare so well once it had become a salmonella virus. An even more extreme (but not unique) example to be given later, involving anthrax before and after its adaptation to rabbits, will illustrate the worst-case scenario most starkly. It is reasons like these that make the transfer even of innocuous-seeming agents quite dangerous: what is innocuous when it is unadapted to human beings may become anything but, afterwards. This is why the possibility that *Clostridium difficile* has only recently become a truly human infection is so worrisome. As it adapts through further human-to-human passages, it has at least the potential to become far more infectious and more virulent to ordinary people than it currently is. Moreover, it is already resistant to most antibiotics and is rapidly acquiring further resistances. It is clear that MAC is not currently a human-adapted infection. But if AIDS should allow it to become one, it will likely be considerably more dangerous than *C. difficile.*

Mycobacterium bovis is the tuberculosis of cattle. It can be transmitted to people through unpasteurized milk. Before AIDS came along, it very seldom spread person to person. However, it can and does spread through the air among AIDS patients (Nitta et al., 2002; Biet et al., 2005; Bouvet et al., 1993). It seems very likely to become able to infect the general population unless its closeness to our own highly-adapted *Mycobacterium tuberculosis* keeps it out. Our own tuberculosis may also make it more difficult for the *Mycobacterium avium* complex and similar mycobacteria to gain a foothold, but these are much less close relatives (Biet et al., 2005, p. 413) and any such effect is likely to be small.

6. Parallels

The attack by AIDS on the immune system of the individual has interesting parallels with its attack on the immune system of the species.

6.1. AIDS' attack on the individual immune system

When a body is first infected with perhaps a single clone of identical HIV virions (virus particles), the immune system seems to handle it successfully. The high initial levels to which the virus grows, often causing a severe flu-like illness shortly after the first infection, are quickly brought down by the immune system. It reduces the virus to such low levels that all symptoms vanish and the victim appears to have fully recovered. But though the immune system has greatly reduced the virus, it has not eliminated it. It continues to reproduce, at reduced levels. And so long as it is reproducing, it is evolving, adapting itself to the particular human body it finds itself in, and to the particular tissue within that body. Virions in the brain adapt to brain tissue and become noticeably different, and noticeably better adapted to that tissue, than virions growing in the lymph nodes or other tissues. The same holds true for virus growing in lungs, the male genital tract, blood, and probably other tissues as well (Connor, 1986; Leigh Brown and Holmes, 1994, p. 156; Ait-Khaled et al.,

1995; Singh et al., 1999; Pillai et al., 2005). This could not occur if countless millions of random variants were not produced from the original single clone.

Such rapid evolution, the most rapid of any organism known, also results in adaptation to that particular person's immune system. The single initial clone becomes millions of slightly-different lineages of HIV, expanding and spreading out, with the passage of time, into forms ever more divergent from the virus that started the infection. And after a while a variant will emerge that has diverged so far from its parent stock that the immune system no longer recognizes it as the same virus. This variant can therefore grow freely, reaching high levels within a few days, until the immune system detects this *new* intruder and mobilizes its response.

With relative ease, the immune system knocks down the variant, just as it did for its parent, and for all its other relatives who have continually been held in check. But again, the immune system fails to eliminate the new virus. As more time passes, the variants become more and more numerous, diverging further and further all the while, and producing escape mutants more and more frequently, mutants which escape immune system detection until they have multiplied enough to present a threat.

There is no limit to the number of such mutants that this single clone of HIV can eventually evolve to produce. And while the immune system may be quite amazing and adaptable, it does have a limit. After a variable period of time, averaging somewhere around 10 years, the number of escape mutants grows so large and so diverse, and their ever-increasing rate of occurrence becomes so frequent, that the immune system cannot keep all of them under control. Sometimes these uncontrolled mutants cause brain damage, which may be fatal. Sometimes they cause lung damage, which may be fatal. At the same time, these least-controlled variants kill certain cells of the immune system faster than new cells can be produced. When too many of them have been killed, the body falls prey to opportunistic infections, which at first it may defeat, or hold in check, but which ultimately, as the immune system continues to fail, become too much. This is how the great majority of victims die, at least with HIV in its present, ever-adapting, highly-protean, form, acquiring greater and greater genetic variation with the passage of time, becoming a more and more complex and formidable super-organism with every passing year, as it slowly engulfs humanity.

6.2. AIDS' attack on the species immune system

Consider now the effect of HIV not on a human individual but on the human species. Even though there are several distinct varieties of HIV, only one, HIV-1 group M, makes up the overwhelming majority of cases. It is the one I am referring to when I say HIV. On the few occasions that I need to discuss one of the uncommon variations, I will be careful to spell that out [14].

If the human species is compared to a single human body, then we are still at an early stage of the infection. Most of the parallels I shall draw below have not yet happened. Perhaps I am wrong and they will never happen. But the potential is clearly there.

Some decades ago HIV entered our species, perhaps as a single clone. It spread around the world before medicine finally detected it in 1981. Shortly thereafter work was started on a vaccine; however, a quarter century later the effort has produced almost nothing.

Nonetheless, some of the failed attempts came close enough to lead me to think that a vaccine may be possible.

But all this while, and in the years before detection, the virus was evolving, diverging more and more from its original form, becoming better and better adapted to human beings, and spreading out into an increasingly varied range of progeny. Today the most divergent descendants of the original virus from a few decades ago differ from each other by more than 40 percent in some of their gene proteins [15]. It seems highly unlikely to me that a single vaccine, even if it is as effective as any vaccine can possibly be, is going to be able to cover this wide variation. So, like the immune system, we will develop other vaccines for the "escape mutants" that the first vaccine fails to stop. But, as in the individual body, the range of variation will just keep growing, and the escape mutants will appear at an ever-increasing rate as more and more strains, further and further apart, come into existence. The current, wide range of variation has emerged from a single clone, or a few closely-related clones, within just a few decades. Within a few more decades, every one of the millions of clones now in existence (every one that leaves descendants, that is) will diverge a further considerable distance. We will have to keep making vaccines at an ever increasing rate. Unless we stop AIDS quickly, within a few more decades we will have been hopelessly outflanked.

There are circumstances where a vaccine strategy could conceivably work, but they require a vaccine *soon* that is able to stop the great majority of the infections. If all but a few divergent strains could be protected against, it might be possible to come up with additional vaccines to handle those few fast enough to beat back the virus. Even if cases cannot be entirely eliminated, if they can be reduced to very minimal levels, they may put out significantly different variants at a slow enough rate that we can keep up with them.

I do not think this is likely. At the present time we do not have even one vaccine effective against even one strain of the virus, and time is decidedly against us. Unless we are able to beat back the virus very significantly and very soon, within another few decades we may well need hundreds of vaccines.

As time passes, AIDS will spread to more and more people, infecting large portions of some populations, certain of which live in areas where new pathogens are especially likely to be encountered. Just as the number of HIV particles in an individual body has to grow to a critical level before its immune system is damaged enough that an opportunistic infection can invade the victim, in most cases it will require a critical density of AIDS victims, a density great enough to allow maintenance of a new infection in their midst for at least a few generations of spread, and perhaps for many generations, before such an organism can successfully invade our species as a whole, becoming an opportunistic infection of the immune-deficient human race.

At an unknown, but almost certainly nonzero rate, a rate that will rise as larger and larger areas of the world attain the requisite AIDS concentrations, new pathogens will be transferred into our species through the breach in our species immune system that these AIDS cases constitute. Most of these new pathogens will turn out to be minor – just one more cold variety or 24-hour virus. But if there are enough of them, eventually we shall hit an Ebola or Marburg, or one of the slow viruses of monkeys that cause immunodeficiency when they infect new species. Or maybe just bird flu.

These are the opportunistic infections that cannot infect humanity when it has a healthy species immune system. As AIDS cases grow ever larger, the species immune system grows progressively weaker. In the case of the infected individual, opportunistic infections

eventually prove fatal. It may be unlikely that opportunistic infections will ever prove fatal for our entire species, but they could reduce us to a small remnant, and they could certainly prove fatal for our civilization. Perhaps civilization could survive one great planetary catastrophe, but what about half a dozen in a century? It could be much worse than that. No one knows how many pathogens may be *nearly* able to infect our species now. Will the breach allow in one, ten, a hundred new diseases? And how bad will the worst of them be? A single one, if it is bad enough, could represent a death blow for our civilization. Indeed, the great question is whether a single one, HIV, already has.

There is one final potentially important point for which there is no parallel. It is possible that the first really bad fast-spreading epidemic we encounter, bird flu or Ebola or Lassa or some currently nameless pathogen we are not even aware of, will kill HIV victims far better than it kills the uninfected. It is possible it could reduce HIV infections to a remnant. This would substantially repair the damage to the species immune system, and if we could thereafter keep the few remaining HIV cases under control, might allow us to escape with just one terrible episode.

The reason this is not likely is due to the long incubation period of HIV. The new pathogen would probably only preferentially kill those whose immune systems were failing, and that would be a distinct minority. Therefore, it is unlikely to have any significant effect, though I can imagine cases where it would.

In order for there to be a parallel in the case of infection of the individual, it would be necessary for one of the opportunistic infections that AIDS allows into an individual human's body to preferentially attack cells that were infected with HIV itself. At present there are no such opportunistic infections, though I do not see any reason in principle why such a thing could not happen. I cannot see any reason in principle why one of the new opportunistic infections our species falls prey to as a result of its weakened species immune system could not constitute such a remedy, repairing the damage that enabled it in. But the odds are surely thousands, and probably many thousands, to one against it.

7. How many new diseases?

That AIDS represents a door through which new diseases may enter our species, and that they may persist even if HIV is one day eliminated, is a simple proposition whose truth can scarcely be gainsaid. But the number of new diseases that are able successfully to slip through this door is a much more difficult question. Perhaps it will be zero. Perhaps it will be hundreds. Perhaps somewhere in between.

In the previous section I claimed that the number would almost certainly be greater than zero. In this section I attempt to defend that claim.

I can think of four significant reasons bearing on the question. The first three each lead one to believe the number of new diseases will be very large. The last reason gives some grounds to hope the first three may have overstated the danger. But the last reason, itself, though significant, may be less significant than it first appears.

7.1. Reason 1

Consider the following analogy: We can picture the species immune system as a high wall surrounding our species, and all around the wall are several millions of different types of microbes, habitants of other species, jumping as high as they can to get over the wall in order to infect us – one of the most massive food supplies in all the animal kingdom. And even though there are millions of different types of microbes, not a single one of them can jump high enough. But we know that some of them can jump *almost* high enough by the simple fact that there are many microbes that in the past have successfully made it over the wall. The wall is not so high that to cross it is impossible; rather the height of the wall has determined which microbes made it over: those that could jump high enough did, leaving those that could jump almost high enough (and all the rest) behind. There are too many of these different microbes for the range of heights to which they can jump not to be practically a continuum. Therefore, any lowering, if it is at all significant and if it is sustained, will let over all those that can reach the new, lower height. And it will not be zero.

It is also clear that the number that can cross over will not be proportional to the lowering, but far more. If a 1 percent lowering lets 5 microbes over, a 2 percent lowering will not result in 10, but perhaps 50 or 100. The number of 8-foot high jumpers in the world is 1. The number of 7-foot high jumpers may be a few hundred. But the number of 6-foot high jumpers is surely on the order of a million.

To take the analogy one step further: The height of the wall is not exactly the same everywhere. Perhaps somewhere along its circumference a single brick has fallen off the top. Given enough time, all organisms that can cross over that lowest point will make it over. But the organisms are blind and can only make it over if they happen to be jumping in exactly the right spot. The height of the lowest point determines which organisms can get across, but the width of this lowest point determines the rate at which they will cross over. If the low area makes up half the wall, it will take twice as long as if the whole wall were that height, because half of the jumps will be at a spot that is too high for the organism to make it over. And each AIDS patient can be thought of as a tiny low-spot in the wall. When there are only a few AIDS patients, it might take thousands of years for one of the few highest-jumping microbes to encounter such a low spot. But each doubling of AIDS cases will halve that time.

However, that is only true when the density of AIDS cases is low. At high density, interactions among AIDS patients will result in a significant further lowering of the wall. It is the patient-to-patient transmission among AIDS cases of varying severity that allows the time and the teaching of the microbes to infect our race. A certain number and density of AIDS cases, different for every potential new microbe, will be necessary before most of the prospective new diseases can be passed enough times to become able to infect the non-AIDS population. Probably only a very small minority of all the potentially-successful microbes will be able to infect the normal population after passing through just one AIDS patient. Therefore, a doubling of AIDS cases will likely much more than double the rate and much more than double the ultimate number of microbes that can make it across. A doubling of cases doubles the rate at which microbes make it into the first AIDS case. But the simultaneous doubling of density increases the lengths of the longest AIDS-to-AIDS chains, and thereby greatly increases the number able to leave the AIDS chains and infect

the rest of the population. And doubling the density does more than just double the length of the chains. Indeed, for many of the pathogens, at some critical density of AIDS cases the transmissibility will go from below 1 to above 1, and the chains will be able to persist indefinitely.

Any clustering of cases will likely make things worse, through this more-than-proportional density effect. This is not 100 percent clear, however, since clustering will also reduce the number of different microbes that encounter AIDS cases and make it into their first human.

7.2. Reason 2

Many of our most serious infectious diseases, including the number one killer of all time, smallpox, and number two, tuberculosis, have come from our domesticated animals within the last 14,000 years (or whenever domestication in fact began). The animals that have been domesticated are an infinitesimal fraction of the animals that exist. The contacts that successfully transferred these terrible diseases were entirely natural, without the millions of AIDS cases and other recent decrements to our species immune system (to be discussed shortly) to offer assistance. It is extremely likely that some of these transfers were one-time events. By that I mean in some of these transfers, if the person who first became ill with the new microbe that he and those he infected then passed on enough times to become a new human disease, had not gotten infected, then we would today not have that disease. All of the cases before (by hypothesis) and all of the cases caught directly from the animal since, would have failed to transfer the microbe enough times to enable it to become a persisting human infection.

Recall the simple calculations we did regarding the number of bird flu cases that must be caught directly from birds before enough adaptation to humans can occur to make an epidemic likely. That number was very highly dependent on the number of times bird flu must be successively passed human to human in order to adapt and on the chance that a case caught directly from a bird would pass it to a second human. With just the small range of 4 to 9 passages and 5 to 15 percent chance, we got estimates ranging from less than 150 to over 2,000,000. Among the animal pathogens that can, potentially, ever naturally adapt to become human infections, those that need 12 or 15 successive passages might easily require hundreds of millions, or even many billions, of cases caught from animals before 12 or 15 successive passages would become likely. And what of those that could become human pathogens but would require 20 or 200 passages? Most of these potential pathogens have never (yet) managed to infect anywhere near the requisite number of humans. Most of them are still animal microbes which have never managed to jump over the wall.

But when we have very many such microbes, even though the odds of any particular one making it over the wall may be small, it is likely that a few will succeed in crossing over, just by chance – even a few of those requiring hundreds of millions and perhaps billions of cases to make it *likely.* These are purely chance occurrences, and it is probable that there are other pathogens that had just as good a chance, or even a significantly better chance, that never made it over. It is probable that many of the transfers from animals are slow, random events and that we have so far seen only a fraction, perhaps a small fraction, of the diseases that are *able* to make it over and that ultimately *will* make it over given

enough time.

Let us ask: Under natural conditions (without AIDS, etc.), of the diseases that would ultimately be transferred into humans from domestic animals, what fraction would be transferred within the first 14,000 years? The answer is not at all clear, not even whether it would be a large fraction or a small one. Suppose there are 100 animal microbes that each stands only a 10 percent chance of crossing over within the first 14,000 years. We will expect 10 of them to do so in those 14,000 years, leaving 90 just as able, all of which, given enough time, will be transferred later. On the other hand, perhaps there are a few microbes that can be transferred easily, and have therefore all been transferred long ago, while all the rest are hopeless cases that could never infect our species. So far, we have seen about 10 percent of those which stand a 10 percent chance of transfer within 14,000 years, 5 percent of those which stand a 5 percent chance, etc. But it is very difficult to say how many belong in each category, or what the total of all the categories comes to.

The various decrements to our species immune system, including especially AIDS, will vastly speed up the rate at which these *able* pathogens make it over. But they will also enable many others, not previously able to make it over, no matter how much time they were given, to do so.

Thus, under the assumptions we made about bird flu, we found that each 2-step increase in the number of necessary passages, multiplied the number of cases needed by roughly a factor of 10. If 200 passages were required, the factor of increase (over a variety requiring 9 passages) would have been greater than 1 with 95 zeros, and natural transfer is utterly impossible.

This 10-fold multiplication occurred when we assumed that a person infected by flu caught directly from a bird had a 10 percent chance of infecting another person. Therefore, we implicitly assumed a similar 10 percent chance in arriving at our number of 1 with 95 zeros. But suppose the average AIDS patient infected directly by a domestic animal infected an average of 1.0 further AIDS patients. Even much more than a factor of 10 increase due to AIDS is easily possible, and with it the 200 passages necessary to adapt the pathogen to spread within healthy human populations become easily possible, at least if there are large enough concentrations of AIDS patients to permit the new pathogen to continue to circulate within them [16].

7.3. Reason 3

Among the animal pathogens that can adapt to our species with just one or two human passages, a significant proportion have already made it over. When we think of those requiring 8 or 10 passages, some will have made it, but the large majority likely will not have. When we get to pathogens requiring 20 or more passages, it is likely that very few of them have already managed to become human infections.

Consider now the numbers of potential pathogens falling into each category. There are surely *many times the number* of potential pathogens which could succeed in 20 passages compared to the number that could succeed in 10. (It is rather like the case of the 8-foot high jumper.) The same is surely true with 50 passages as compared with 20. I suspect it is true for 100 and quite probably 200 passages as well, though after some large number of passages, we are likely justified in concluding that it will never succeed however many

chances it might be given. Thus it is probably correct to conclude there are *far fewer* potential pathogens that would require 10,000 or more passages to adapt to our species than could do it in 200.

AIDS makes possible even more than 200 person-to-person passages, so that instead of zero percent of those needing, say, 50 or more passages to adapt to our species, given enough time we can expect a non-negligible fraction to succeed. And because of the huge numbers of potential pathogens needing large numbers of passages, completely swamping the numbers of those needing only a few passages, we may find that the new pathogens entering our species via this route are predominately those that were unknown or seemed least likely. Even 200 passages of a rapid-acting microbe such as the flu can require only two or three years, but 200 passages of one of the slow viruses might take centuries. So there may be a change-over with passing time among the sorts of new pathogens acquired through this route. In the beginning there will be the infections that were foreseeably a problem: those nearly able to survive without the help of AIDS, those needing just a few passages to adapt. These may be predominantly the rapid-acting infections, but slow viruses that need only two or three passages to adapt, such as quite possibly some of those inhabiting our close kin, the apes and monkeys, could also enter rather quickly. HIV has now been in our species for at least 50 years, and that is long enough for 5 or 10 passages of even most of the slow viruses. However, for most of that time, the numbers of AIDS cases was too small to make person-to-person transmission very likely.

That is now no longer true, and we are nearing the point that the best candidates among the slow viruses could start succeeding. To begin with, these may be viruses such as the many SIVs and SRVs that could have been predicted. But in another century, the new diseases that enter through this route will likely come from far less foreseeable sources.

I am saying, in other words, that we are very likely to see at least several new human diseases emerging from the AIDS epidemic, coming just from our domestic animals. And when we consider the countless thousands of non-domesticated animals that humans occasionally come into contact with, the hope that AIDS may present only a theoretical danger, but not an actual one, seems quite farfetched. Just in the last few years, we nearly saw the start of a terrible new human disease coming from such an animal (a type of civet), without any help from AIDS, in the case of SARS. It is my view that we escaped a catastrophic worldwide pandemic by only a hair. It was stamped out quickly, before it could possibly have reached its ultimate transmissibility among humans. Yet this was done with great difficulty. Had it been more transmissible by any significant amount, it would have been well beyond our capabilities. With AIDS, and with the other assaults on our species immune system to be discussed in the next section, now assisting would-be pathogens, we will not always be so lucky.

And though I have several times specifically mentioned the millions of animal microbes, we should keep in mind that there are also countless others that live in soil or water or on plants; and while they may have more difficulty adapting to our species, they still have the potential to do so if they can even rarely infect AIDS patients and even rarely spread patient-to-patient.

7.4. Reason 4

The final reason is more optimistic, and might be cast as an objection to my concerns: "The process you describe for adaptation to the general population via the stepping-stone of AIDS victims is frightening, but you have greatly overstated its magnitude. Despite the severe and ultimately fatal immunodeficiency that develops in AIDS victims, in fact the number of opportunistic infections they fall prey to is relatively limited. It is not the millions of non-human microbes that AIDS now puts the general population at risk for, but only the few dozen that are managing to successfully infect AIDS patients. The danger is real, and it may be considerable, but it is not the horrific picture you paint."

As I said above, I think there is a fair amount of validity to this objection; but it, itself, is overstated.

There are two points to be made. We are not so much concerned with the number of non-human microbes that *commonly* infects AIDS patients as with the number that infects them in total, i.e., with even the very rare infections that manage to succeed in only one AIDS patient in a million, or many million. This is a far larger number, and I suspect it may well range into the thousands. Once the first patient is infected, there is a distinct chance the pathogen will adapt in the course of that one infection well enough to be able to infect a second patient with an advanced case of AIDS. The greatest effect of rarity will be to reduce the rate at which new infections enter the general population. But, given enough time, it is likely that a similar proportion of the rare as of the common infections will ultimately make it, and we have a far larger number to pick from. Therefore, most of the infections the population as a whole ultimately falls prey to may be unknown or little-known infections that hit us out of left field. And some of the rapidly-adapting ones may strike with very little warning. SARS is a good example of a previously completely-unknown disease that came out of nowhere. If it had not been very promptly stopped, it might well have killed tens of millions within a year. SARS had nothing to do with AIDS, but that is the sort of thing we may see more often as the density of severely immunocompromised people rises in the world.

The second point to be made is that there may be more opportunistic infections than we know, even more of the common ones. Suppose the new pathogen grows so poorly in its first human victim that it causes no symptoms at all. Suppose it can persist but it will take 50 years before it will have adapted well enough to start producing symptoms. The AIDS victims will have died of other, more rapidly acting, opportunistic infections long before this one shows up. But if it can spread to a second AIDS patient, it can continue its adaptation even after the first has died. Therefore, this initially-benign subset of opportunistic infections is not being counted. A similar argument is discussed in more detail as part of the Appendix.

Perhaps the severest impact of this reason occurs on reason 3. I claimed there that there were likely many times as many microbes that could be adapted to human beings given 200 human-to-human passages, as those that could do it in 50 or less. But reason 4 gives much reason to doubt this claim, or rather the relevance of it, for surely many, and quite possibly the vast majority, of those microbes so ill-adapted as to require 200 passages, are far too ill-adapted to ever infect a single AIDS patient. The requirement that the microbe be well-enough adapted to potentially infect an AIDS patient does drastically reduce the number of new diseases AIDS can transfer in. But if there are a number of these just among our domestic animals, as I think is surely true, then there are likely thousands of times that number among the microbes existing in species or habitats that human beings do not often have contact with but may encounter from time to time. And when AIDS cases reach a

critical density (different for each potential new disease), then even a single instance of such a rare infection will present an appreciable chance of infecting further AIDS cases, and through them the entire species. When AIDS cases reach a critical density, the human race becomes an amplifier of such rare occurrences, a detector of such rare events, which we may find to our chagrin happen more often than we were aware.

8. Other assaults on the species immune system

There are other assaults simultaneously being waged on the species immune system. They all pale beside AIDS, but there are enough of them – and many of them are growing at a fast enough pace – that together they could be quite significant. There is also a substantial chance that beyond these I am listing, other major assaults exist that I failed to think of, perhaps due to simple overlooking, or perhaps because their role is too subtle or too unexpected for my mind to have alighted on them. I did not think of smoking or global warming, and their particular mechanisms, until I was putting the finishing touches on this paper; and while they are perhaps not among the more important, one can see by means of their example that there is a high potential for the existence of other unexpected assaults, some of which may be major.

8.1. Overpopulation

Perhaps the least overlookable of all these assaults, and one of the most significant, is overpopulation, and the results of overpopulation. We have already seen how measles, smallpox, and many of the other short-lived epidemic diseases producing long-lasting immunity were unable to cross over from their original animal hosts into humanity until populations passed a certain level. But these rapidly-spreading, immunity-producing diseases are not the only ones increasing population may allow to cross into our species. For obvious reasons the great majority of contagious diseases are able to spread more easily in denser populations; and likewise the great majority of would-be human infections that occasionally succeed in one person's body but have trouble spreading on from there, will infect more secondaries if there are more and closer contacts. Even moderately greater density may give a new microbe a *far* greater chance of making it through the difficult period before it has had a chance to adapt well to its new species, after which time it may be able to spread into much more sparsely-populated regions.

Greater density, such as is found in the largest urban areas, may be a more important factor than the absolute number of people in the world, but overpopulation is probably the greatest single cause of the rampant urbanization that has taken place over the last century. Overpopulation is also a prime cause of greater poverty, which makes our species less healthy and therefore an easier target – indeed malnutrition, and no doubt other effects of poverty, directly suppress the immune system.

Overpopulation is also forcing the expansion of cities into areas where they are more likely to encounter new animal microbes. If monkeypox infections now die out because

each case infects only 1/2 further case (a number I am just making up for purposes of illustration), and population density suddenly rises to the point that the increasingly close contact among individuals now allows monkeypox to spread to 1.5 further cases, it is easy to see how humanity might thereby gain a new pathogen.

While overpopulation's greatest effect may well be due to increased density, sheer numbers of people will multiply the occurrences of rare events that could lead to infection by novel organisms. I shall discuss the bushmeat trade below, but the several billions of kilograms of meat from jungle animals that the human race now consumes each year would be a lot less if the human population were a lot less.

And while I am chiefly writing about factors that will allow brand new human diseases to get started, it has of course long been recognized that overpopulation will increase the frequency and size of epidemics of existing diseases – with many writers from Malthus on predicting worldwide plagues that will remove the excess population – and this also represents a weakening of the species immune system, at least as I have defined it [17].

8.2. Smoking

Smoking, especially cigarette smoking, may be a relatively small insult to the immune system of the individual, but because so very many individuals are smokers, it may have a fairly significant effect on the immune system of the species, particularly with regard to new diseases that spread via the airborne route.

I have not seen any statistics, but I would guess that a population half of whose adults are cigarette smokers might well cough 10 or more times as much as a population without any smokers. A new organism just barely able to survive in human lungs may produce few symptoms or none at all. Without coughing, it will have little chance to spread to further hosts. Cigarettes might be able to lend a hand and enable these organisms to infect significantly more secondary contacts than they could do on their own. And even if the organism does produce coughing, cigarettes will add still more coughing, perhaps in borderline cases enough to carry the number of new infections from below 1 to above.

Moreover, at least for certain organisms, smokers' lungs are easier to infect in the first place (Sethi, 2000). We saw at the end of Section 5 that the *Mycobacterium avium* complex (MAC) was one of the bigger risks for developing the ability to spread in normal populations. And while it seldom attacks people with intact immune systems, one big exception is those with certain sorts of lung damage, especially chronic obstructive pulmonary disease (Field et al., 2004; Aksamit, 2002). Smoking is the largest single cause of COPD.

Since *far* greater proportions of AIDS victims are infected with MAC than are smokers, it is likely that if MAC does ultimately become an infection of the general population, it will be due to AIDS rather than smoking. On the other hand perhaps neither one by itself would be sufficient, but AIDS victims who smoke, or AIDS victims in populations who frequently cough because of smoking, will together manage to adapt these new and very hard to treat tuberculosis-like organisms to the general public, enabling them to infect even those who live in societies without any AIDS or smoking.

Indeed, anything that increases coughing will likely increase the amount of coughed-out new pathogens, and among the most obvious of these causes of increased coughing are

respiratory infections themselves. In some cases the activation of the immune system caused by ordinary respiratory infections may make it harder for ill-adapted new microbes to survive, but in other cases effects of the ordinary pathogen may make it easier. The suppression of the immune system due to AIDS will clearly assist most prospective new microbes in growing within the respiratory system, while the increased coughing produced by TB, pneumocystis pneumonia, other AIDS-related respiratory infections, and indeed the effects of HIV itself on the lungs, will help with spread to new individuals.

Tobacco use may have been around for hundreds of years, but not until the early twentieth century and World War I did a substantial fraction of the public take up cigarette smoking (Whiteside, 1971, pp. 9-10). Cigarette use in developed countries is now waning, but numbers of smokers continue to increase in the less developed countries, and especially in Asia. Air pollution acts in a very similar way, and it is growing rapidly, again, especially in Asia.

8.3. Global warming

Air pollution also increases global warming, and this will change the geographical area where vector-borne diseases and some others can exist. The thousands of years of exposure to malaria has caused African populations to evolve resistance mechanisms (the best known of which is the sickle-cell trait but there are undoubtedly many others) which are lacking in populations located too far outside the tropics for malaria mosquitoes to survive. As tropical climates expand, these nonresistant populations will be exposed to potential pathogens they were never exposed to before. Perhaps some of these potential pathogens, especially (in this particular example) close relatives of human malaria, have never been able to become human infections because the evolved resistance to human malaria was enough to make their precarious early passages impossible. But perhaps they could survive, and ultimately adapt, in populations without these resistances to malaria. And once adapted, and far better able to survive within humans, they might well be able to infect even the resistant African populations.

In a similar way, increased volume and speed of travel might transport non-human microbes from societies they cannot invade, because of those societies' genetically selected immune adaptations mirroring the constellation of microbes their ancestors were exposed to, or because of individually acquired immunities owing to the infections they themselves have experienced, into other societies that are easier targets. This also applies to globalization in general, with shipments of food and other items perhaps transporting bacteria, fungi, arthropod vectors, etc. from areas where they are endemic to those where they have never been seen before.

8.4. Medical dangers

Earlier I mentioned babies born with serious genetically-caused immune deficiencies. They have always existed in extremely small numbers, but today there are far more

non-HIV-infected people with differing levels of immune deficiency due to certain medical procedures that have arisen largely in the last few decades. In Section 5, I discussed one important example, those whose intestinal immunity had been severely impaired by antibiotics, and the possibility that *Clostridium difficile* and other microbes were adapting to normal populations through spread among debilitated patients treated with antibiotics. The debilitated *aged* are especially susceptible.

8.4.1. The aged

Medicine now keeps people alive who in earlier times would have died. As we age, our immune systems naturally weaken and we become prey to some of the same opportunistic infections that afflict AIDS patients. Modern medical procedures can repair some of these immune system weaknesses, so that by the time we finally die, our underlying immune systems – what would exist in the absence of medical intervention – may be weaker than would ever have been possible in earlier times. But the repair does not exactly replace the damage. In some respects, the repaired immune system may actually be stronger than the original, but in other respects it will be weaker. It is rather like building the wall of the immune system higher in some spots, but reducing its height in others. Even if the average height is the same as before, indeed even if it is far higher than before, so long as the lowest point falls below the previous low point, there is potential for new microbes to jump over. Here, the wall is the individual immune system, but any weaknesses there also form weaknesses in the wall of the immune system of the species.

And, of course, concentrations of debilitated elderly people in old-age homes or geriatric wings of hospitals allow for the spread of an opportunistic infection from one individual to another. In previous generations, these concentrations were a tiny fraction of the size and number that exist today.

I have not looked into this case in any detail. My feeling is that the difference in numbers and immune deficiency of the debilitated elderly are not such great changes as to constitute a large threat, compared to most of the other threats to the species immune system. But when this is combined with the clustering together, it becomes a greater threat. I earlier described antibiotic-caused destruction of the friendly intestinal flora as the chief factor in the development what may well be a new human disease, the specifically human strains of *Clostridium difficile* that now exist. But the presence of *clusters* of susceptible individuals may be just as important a factor as the antibiotics, and more important than the actual numbers of susceptibles. A few hundred susceptibles in one cluster may be more important than a few million scattered randomly about in no clusters of any size.

8.4.2. Cancer therapy, transplantation, and xenotransplantation

Certain cancer therapies, such as bone marrow transplants and many forms of chemotherapy and radiation, greatly suppress the immune system. Usually this is only temporary. Other medical procedures, notably organ transplants, deliberately suppress the

immune system permanently in order to prevent rejection of the transplanted organ. There are growing numbers of these patients, and they perform much the same role as AIDS patients in the weakening of the species immune system, the chief difference being in their much smaller numbers, and in there being no significant group of needle-sharing IV drug users among them.

But among the transplant patients, there is one special category which is far more dangerous than all the others, a category which, patient for patient, is a much more serious threat to the species immune system than someone infected with AIDS. Fortunately, this category is so far very rare.

I am speaking of xenotransplant patients, those receiving their new organs not from a human being but from an animal. If I were a mad scientist plotting to start a new plague, one that would kill and kill and keep on killing down the generations, I could hardly do better than to take a whole organ, weighing perhaps hundreds of grams, from an animal (the more closely related the better) and put it inside the body of a human being, then suppressing that person's immune system and keeping it suppressed for years or decades while the animal's microbes – which initially perhaps can survive only inside the animal organ – slowly adapt themselves to the immunosuppressed human body they now find themselves surrounded by. I would still have to take that microbe and adapt it to less immune-suppressed individuals, but here the AIDS patients, if they are numerous, will come to my rescue. Or perhaps the patient, so grateful for having had his life saved by a transplant, will donate his own organs upon his death to be transplanted onward. Or perhaps he will donate blood for a transfusion.

It is a brilliant scheme, but there is one way to do it even better: If I can achieve a great success with this organ transplant procedure, doctors everywhere will copy me. Instead of just one chance, or a handful of chances, there will be thousands of doctors all over the world helping me succeed. Perhaps in attempting to start a single plague, I have set my sights too low. Perhaps I can start a dozen. (And, with any luck, I will get a Nobel Prize in the process!)

In all seriousness, if I truly, truly did my best to come up with a scheme for starting new diseases, I am not certain I could top that one [18]. It is a measure of the stunning ignorance of evolutionary considerations that pervades the medical profession that permitting such a thing was ever even contemplated. That it should occur after AIDS has shown us what a new animal disease can do to our species is simply beyond belief. (But then AIDS has hardly started showing us yet.)

8.4.3. Transfusion

There is another medical diminution to our species immune system that is far more common than any of these others, with the single possible exception of the debilitated elderly. Indeed, I just mentioned it three paragraphs above: transfusion. This permits a new organism, which is well-enough adapted to be able to survive, perhaps with difficulty and in small numbers, within a human body it has somehow managed to infect, to spread to another human, when it is not yet nearly well enough adapted to spread naturally. Perhaps the additional time spent in the recipient of the transfusion will suffice to achieve the necessary adaptation, but probably more frequently, the microbe will have to be assisted

again.

Donating blood is quite common, and I suspect it is far more common among those who have their lives saved or their health restored by a transfusion. Of course, the health of many transfusion recipients is too precarious to enable them to donate blood. But many others are young, healthy automobile accident victims, or soldiers wounded in war, who potentially can donate many times during the remainder of their lives. I would be willing to bet that the average number of blood donations from such recipients exceeds 1 by a considerable margin. If it is a large enough number to save the life and restore the health of 1 further young recipient, on average, then we have conditions that will allow the maintenance of the microbe within this population, perhaps indeed within growing numbers of this population, until – perhaps decades or even centuries later – its increasing adaptation allows it to begin to spread in other ways.

How might the foreign organism get into the original blood donor in the first place? There are many ways a very rare anomaly can result in an infection of a single individual, somewhere in all the world, with a microbe that does not normally infect human beings. Such cases are usually not a serious concern because seldom will such an infection achieve sufficient adaptation to infect anyone else. Now that AIDS is here, the concern becomes much more serious. And transfusion is yet one more way the new organism can spread to a second person and acquire more time to adapt.

AIDS, IV drug abuse, and transfusion may frequently interact. An AIDS patient who has picked up a new, nonhuman microbe, perhaps shares needles with a non-HIV-infected person and thereby manages to infect him with the new microbe (but perhaps not with HIV, which is not so easy to catch through a single sharing incident with an AIDS victim). Like a great many IV drug users, he sells his blood to get money for drugs. They test his blood for HIV, but not, of course, for the new microbe. Perhaps that is how the original transfusion recipient became infected.

Transfusion, because it is so common, and because it involves a large transfer of potentially infected material, completely bypassing one of the most important components of the immune system, the skin, and because the recipient may often be in a weakened state that assists the new infection, represents an appreciable injury to the species immune system. It would not surprise me if several diseases had not already entered via this route, or this route in combination with others.

Stopping xenotransplantation can be accomplished with great benefit to the species and with harm to but a few. Transfusion, on the other hand, would be terribly painful to stop. But fortunately, a substantial part of the danger from transfusion can be removed through one simple and almost painless step. In addition to the diseases such as hepatitis B or C that make one ineligible to donate blood, add the condition of ever having had a blood transfusion oneself. That will limit the spread of a new organism via transfusion to one additional person. The great majority of the time, that will not be enough to allow the organism to escape into the general population [19].

Also, anyone ever having had an organ transplant, or any other procedure that even temporarily caused a serious suppression of immunity (during which time the person could have acquired a novel infection), or anyone ever having had a procedure that would allow the easy passage of a new organism that could not be transmitted normally (transfusions are the most common, but there are a number of others, such as being the recipient of an egg donor), should be permanently barred from donating blood or plasma or organs or anything else that would go inside another human being. It is important to realize that a new and

poorly adapted infection may be completely symptomless, or like HIV, cause its characteristic symptoms only after many years, so that neither doctor nor patient suspects a thing. HIV existed as an infection of the human race for over 20 years and spread around the world before the first case was discovered in 1981. There is at least a small chance that such a rule, back when HIV was least well adapted and perhaps barely holding on, would have stopped it. (And we would never even have known what we avoided.) Such rules would diminish the blood and organ supply only marginally, but might greatly reduce the transfer of new diseases into our species via these routes, quite possibly by 90 percent or more.

And more money should be spent on developing artificial blood substitutes for use in transfusions. And until this is accomplished, more emphasis should be put on storing up one's own blood to be transfused back.

8.4.4. Reused needles

Two other threats to the species immune system, again as a result of medical advances, require mention. Marx et al. (2001) show that the reuse of unsterilized hypodermic needles meant for one use only was so widespread in Sub-Saharan Africa in the 1950s, with over 75 percent of households receiving an injection over any two-week period, largely from needles that were unsterile, and with 80 percent of Ugandan households having their own household needle, that they suggest this as the means whereby HIV was artificially passed person-to-person enough times to change from a simian microbe occasionally infecting a single human being but too poorly adapted to spread to the rest of the population, into a truly human pathogen. They say needle misuse is still widespread and growing, and not just in Africa.

This is obviously very similar to my speculation above about transfusions; each complements the other. Transfusions transfer well over a million times as much blood [20], and there will be organisms that could not be transferred with the tiny dose from an unsterile needle. (One must get the transmission rate above 1.0 before the sporadic chance infection has died out – even today only one in several hundred accidental needle-stick injuries involving HIV-infected blood results in HIV transmission, and Marx et al. are supposing (almost certainly correctly) that the original HIV would have been significantly less transmissible than today's. Nevertheless, it is possible that substantially more blood would be transferred in a deliberate medical reuse than in an accidental needlestick, which is probably removed within 1/5 of a second, on average.) But those microbes that can be so transferred will find dozens of times as many opportunities through needles as through transfusions.

Another difference arises from considerations of time. Most infections last only a short time before the body overcomes, and completely exterminates them (or vice versa!). They will not be around any more by the time the person who got the microbe through a transfusion has recovered enough from whatever necessitated the transfusion to be able to donate blood. This is the sort of infection that can best make use of reused needles. It is only the persistent infections that can benefit from transfusion, and the microbes that are newly transferred into our race through transfusion will mainly be the ones that last a lifetime, or at least for some years.

8.4.5. Contaminated vaccines

Interestingly, Marx et al. propose their mechanism of reused needles in an attempt to escape from the dire possibility that HIV instead arose from a contaminated oral polio vaccine – the second of the two remaining medical dangers I alluded to. This highly contentious issue is forever being proclaimed dead only to rise up Phoenix-like when shortcomings of the various refutations are pointed out [21]. I certainly can't cover this large topic here, but instead point to the critical importance of a matter on which both sides are in agreement: Whether or not that is how AIDS started, AIDS clearly *could* have started that way, and other viruses clearly *did* infect humans, both from contaminated polio vaccine and from other contaminated vaccines.

Live virus vaccines are particularly vulnerable, because procedures adequate to kill all contaminating viruses (including viruses that are undetected because they are unknown) cannot be run: such procedures would kill the vaccine virus and destroy the vaccine. But inactivated vaccines are also vulnerable, since too much inactivation will destroy these vaccines as well. Consequently, there remains a danger that the inactivation used to kill the virus that is meant to be in the vaccine will prove inadequate to kill the virus that is not meant to be there. Both Salk's killed polio vaccine and Sabin's live one given before 1963 were frequently contaminated with the SV40 virus of macaque monkeys, from the macaque kidney cell cultures the vaccine virus was grown in. Salk's vaccine was first licensed in 1955, but SV40 was not discovered until 1960. Many millions of Americans and millions more around the world were infected with SV40 (Shah and Nathanson, 1976; Bookchin and Schumacher, 2004).

Though it causes no symptoms in the vast majority of those who get it, SV40 is highly carcinogenic in hamsters and several other species, causing, for example, mesothelioma in 11 out of 11 newborn hamsters injected with it (Bookchin and Schumacher, 2004, p. 142). There are three other types of cancer frequently seen in hamsters as a result of SV40, and all four types of cancer, but especially mesothelioma, have now been linked to SV40 exposure in human beings. A number of other cancers, especially several different cancers of the brain, have also been strongly linked with SV40. Moreover, SV40 has been found to disable several different anti-cancer mechanisms in human cells and to positively promote cancerous transformation of human cells in several other different ways [22].

Though various powerful entities, mainly in the U.S., such as the CDC, NIH, NCI, and FDA, have claimed the evidence for human cancers caused by SV40 was too weak to be taken seriously, Bookchin and Schumacher (2004) present a massive body of evidence that this claim is untenable, with ten times as many labs finding an association with human cancer as failing to find an association, and with obvious deficiencies in many of the negative studies that can account for their failure. Moreover, the U.S. government and those organizations listed above were grossly negligent in allowing release of vaccines they knew to be contaminated with SV40, so they have good reason to try to cover up the damage they knowingly risked causing, indeed, to try to conceal it even from themselves.

According to official government sources, U.S. vaccine produced after 1961 was free of SV40; however, contaminated batches produced earlier were allowed to be used until their expiration date in 1963. Since SV40 is turning up in childhood cancers today, decades after 1963, and since it has been found in human semen and urine, there is much reason to believe that SV40 is now spreading person-to-person. However, this is far from proven because Bookchin and Schumacher (2004, pp. 267-271) show that: (1) the methods used to

detect SV40 in vaccines would have failed to catch slow-growing strains, and (2) even when they were caught, the known-to-be-contaminated vaccine was sometimes used anyway, at least as late as the late-1990s.

Even if SV40 is now spreading person-to-person, this is not enough to show that it has become a human infection. This is a persistent virus, and even if each case infected only 1/10 further case, and even if all transfers from monkeys ceased after 1963, since there were many millions of initial infections, there would still be many new infections going on. The question, as always, is whether the transmission rate will reach 1.0 before the cases fall to zero. It may or may not be above 1.0 already. I do not think anyone has investigated this important question at all.

If the rate is already as high as 1.0, then this is clearly a new human pathogen that was transferred via contaminated vaccines (two different major vaccines plus several adenovirus vaccines given to military recruits). If it is still below 1.0, and unable to increase its adaptation fast enough to succeed on its own, then SV40, with millions of human infections still extant, becomes one of the best candidates for a new disease to get started via transfusion. Should the latter occur, it will mean that two different triumphs of twentieth-century medicine together teamed up to give us this new human virus.

The question then becomes, regardless of whether or not it causes occasional cancer or other diseases (such as the usually-fatal brain disease progressive multifocal leukoencephalopathy (Weiner et al., 1972)) *now*, what will it be like once it has had enough time to become better adapted to human beings? This is a DNA virus which evolves many times more slowly than HIV. We can say with some assurance that it will become more transmissible as it hones its skills. We cannot say that it will become more pathogenic, but there is a substantial chance of it, as it learns to grow to higher titers in more different tissues. It may be a hundred or many hundred years before the bomb goes off. Or it may never go off. And if it does go off, there is a good chance it will just be a small one. But there is no guarantee; and with several different fatal outcomes already being alleged, the danger is not to be dismissed.

Indeed, after reading the evidence in the Bookchin and Schumacher book I was left wondering why the damage from SV40 is still rather minor today, when it is so deadly in hamsters. In addition to the fact that it has not yet had enough time to fully adapt to our species, I thought of two more-hopeful possibilities: around 80 percent of the population has been infected by one or both of two human viruses, called JC and BK viruses, which are close relatives of SV40. Perhaps millennia of exposure to these viruses eliminated our human ancestors who did not have a strong resistance to them, and perhaps we today are therefore also resistant to their monkey relative. Alternatively, perhaps they act as live-virus vaccines against SV40, just as cowpox acts as a live-virus vaccine against smallpox. Either way, it would be an example of an organism's own pathogens forming part of its species immune system, protecting it against the similar pathogens of other species.

Several other vaccines are also known to have been contaminated with viruses. Yellow fever vaccine uses live virus and – unlike Sabin's live vaccine – is injected, thus presenting the maximum chance for infection by contaminating organisms. Early yellow fever vaccine was contaminated multiple times with hepatitis B and caused the largest known epidemic of that disease, infecting 330,000 U.S. soldiers during World War II (Seeff et al., 1987). At least until the 1990s, yellow fever vaccine was also frequently contaminated with avian leukosis virus, a cancer virus of chickens, whose eggs are used to grow the vaccine virus (Coriell, 1968, p. 185; for 1990s see note [23]). So far as has been reported, no human

being has become infected. It apparently can't grow in humans. But what about humans suffering from AIDS?

A vaccine designed to prevent the sheep disease louping-ill caused a large epidemic of scrapie in sheep in Scotland. The vaccine is manufactured using sheep brains, and some of the sheep used were infected with scrapie but not yet showing symptoms. This is a killed-virus vaccine, but the scrapie agent survived prolonged treatment with 0.35 percent formalin. It infected around 1000 of the 18,000 sheep that received it (Gordon, 1946; Gordon Smith, 1969) and is a significant part of the reason Scotland today has one of the world's highest incidences of scrapie (U.S. Department of Health and Human Services, 1997). Most believe that mad-cow disease was started by cattle being fed ground-up sheep infected with scrapie (Morens et al., 2004). Someone should estimate the degree of likelihood that a contaminated vaccine given in Scotland in 1935 was the ultimate source of mad-cow disease throughout the U.K. in the 1980s and '90s (and the human equivalent, which is still going on).

More recently, scrapie contaminated a vaccine against *Mycoplasma agalactiae* given to goats and sheep. Again, it contained sheep brain, and again it caused a large outbreak affecting over 1000 animals, this time in Italy, starting in 1996 (Agrimi et al., 1999; Caramelli et al., 2001; Zanusso et al., 2003).

This is one of the few areas where insults to the species immune system are decreasing. Today's vaccines are considerably safer than those of the recent past. In the U.S., until the year 2000, polio vaccine was still being made in tissue cultures of African green monkey kidneys (Bookchin and Schumacher, 2004, p. 283), a species that harbors an SIV closely related to HIV, despite the uncontested fact that a similar SIV of chimpanzees had given us AIDS (and the contested fact that it had done so through a contaminated polio vaccine). During the later years of their use in polio vaccine, the African green monkeys were taken from a group transported to the Caribbean during the days of slavery, and it has been repeatedly claimed that SIV does not exist in these Caribbean monkeys. Whether good enough testing has been done to certainly detect an SIV several hundred years removed from its nearest relatives in Africa, and whether enough testing to detect a virus that in its new environment in the Americas, perhaps less hospitable than Africa, might be dying out but is not yet quite gone, seems doubtful. But even if the claim is correct (and while I suspect that it is, I am far from certain enough to risk hundreds of millions of lives on my suspicion!), there are still the other monkey retroviruses, as well as non-retroviruses that might be equally dangerous.

At least as late as 2004 some countries were still making polio vaccine in primary monkey kidney cultures (Bookchin, 2004). I suspect it is still going on today in some of the more remote corners of the world. If so, this may actually be more dangerous for the developed world than if such practices were taking place in their own countries, inasmuch as there is likely to be less testing for known and unknown contaminating organisms, increasing the chances of contamination. Moreover, an unwanted organism making it into the vaccine in a remote area is more likely to succeed in establishing itself as a new human disease, because the public health infrastructure available to either detect it or combat it is likely to be much less sophisticated. A new human pathogen starting anywhere in the world, if it succeeds in becoming established, will almost certainly spread to the limits of the environment in which it can survive. For pathogens that require a particular vector (such as a mosquito), or other specialized conditions, this area may be limited. But for those that can survive worldwide, it is almost surely only a matter of time before they spread

worldwide. A slow-virus infection such as HIV may require a decade or more, but a rapidly-infectious organism such as SARS or Marburg can do it in a matter of weeks or months, and world history might have been very different if either of these two examples had succeeded. Both came close. We should not expect to always be so lucky. We were not so lucky in the case of HIV.

Here a final passage from Bookchin and Schumacher (2004, p. 350) is in order. They are quoting from a 1960 document submitted by Hilary Koprowski and Stanley Plotkin to the World Health Organization:

> Rhesus monkey kidney cultures employed for production of poliovirus have been found to contain a number of viruses grouped under the name of simian agents and to all probability, all vaccine lots fed to millions of people around the world contained at least one of these agents in addition to the attenuated strains of poliovirus.

Koprowski is the researcher who, with the help of Plotkin and others, conducted the world's first oral polio mass vaccination campaign in 1957-58. It was done in Central Africa. This is the campaign that is alleged to have started AIDS (see note [21]).

8.4.5.1. Dangers of making vaccines from primates

Regardless of the specific way in which the several different existing HIV-1 and HIV-2 varieties entered humanity, it is abundantly clear that making vaccines from primates that harbor SIVs has an extremely high potential to transfer them into our species. SIVs cover a great range, and the previously-unknown ones are not easy to test for. When thousands of monkeys are annually being used to make vaccines, as was true for several decades in the last century, it is only a matter of time before one slips through the SIV testing procedure. Murphy et al. (2006) give several different examples of several different simian retroviruses (not just SIVs), that can be present yet fail to be detected by repeated careful testing. Not only were African green monkeys used to make vaccine before SIVs were known, they continued to be used after SIVs were discovered, and this despite the erroneous belief, when it was first found, that the SIV of green monkeys had been the precursor of HIV.

Finally, the argument that the damage has already been done – HIV-1 and HIV-2 are already here; they are now human diseases as well as primate diseases – and therefore we do not need to guard with such extreme care against further transfers, is very seriously wrong. There are at least two strong reasons for this, one of which is easy to explain and one of which is not. I will merely mention, without any attempt to prove, the more difficult one, because the easy one is more than adequate to make the case:

Regardless of exactly when and how it entered our species, in just a few decades HIV-1 has diverged into a large and varied range of viruses (see note 15). Since everyone agrees that the precursor virus has existed in chimpanzees far longer than HIV-1 has existed in humans, it is near certain that the range of variation of the chimpanzee virus exceeds that of the human virus, perhaps by a considerable margin. Aside from the transfer that gave us the main group of HIV-1 (group M), with its tens of millions of worldwide infections, two

other groups of HIV-1, have been discovered. They are known as group O and group N. It is rather clear that these other two groups came about through a further two transfers from chimpanzees (and not that they are just particularly divergent offspring of the original virus that grew into group M). Group O is far commoner than group N, but remains largely confined to Cameroon and a few neighboring countries of West Africa. There are approximately 500 to 1000 times as many group M infections in the world as group O; and at least as late as 2004 only 6 group N infections were known (Yamaguchi et al., 2004; Lemey et al., 2004; Marx et al., 2004).

Group N appears newer than the others (Roques et al., 2004), so there is at least a small possibility that the reason for its rarity is that it has not yet been here long enough to spread. But group O appears to be about the same age as the hundreds-of-times commoner group M (Lemey et al., 2004).

Consequently, among the *great range* of chimpanzee SIVs, there are some when transferred that will manage to infect only a few thousand or a few tens of thousands of people in their first 50-100 years, while others will infect tens of millions. When you have only three transfers to look at, and the range of outcomes has been so vastly different, it is extraordinarily unlikely that with all the diversity in chimpanzees to pick from we managed in the first three successful tries to find the very worst. It is extraordinarily likely that there are still worse varieties existing in chimpanzees, the worst of which may be far worse than any of these three, and we had better guard with extreme care against transferring any more.

Similar arguments apply to the SIVs existing in monkeys. HIV-2, which came originally from the sooty mangabey monkey, though far less bad (so far) than HIV-1 group M, is far worse than group O or group N from chimpanzees. There are almost surely worse, quite possibly far worse, varieties existing in sooty mangabeys that have yet to be transferred. We should take extreme care to make sure that this does not happen, and similar extreme care to see to it that the many SIVs existing in at least 35 other species of African monkeys never get transferred (Apetrei et al., 2004). With all the contacts over the millennia between humans and simians, it is clear that transfer of these SIVs is not easy. But it happened at least 5 times in the last century – at least 3 times for HIV-1 and at least 2 more for HIV-2; moreover, there are another 6 HIV-2 transfers that have been alleged but are known from only one case each, and in my view are not yet proven (Marx et al., 2004; Weiss, 2003b). And in this century there are already millions of immune deficient people who may present an especially easy target for these other SIVs, which, existing in so many different species and evolving so rapidly, must necessarily cover a vast range. And year by year this large number of potential easy targets is growing larger.

The second, more difficult, argument, which I will only give in outline form, makes the claim that another transfer even of the *identical* variety that started HIV-1 group M, would be a potentially catastrophic event. The argument depends on realized and unrealized evolutionary potential and the fact that as unrealized potential is converted into realized, unrealized potential decreases, and especially on the fact that the conversion is not one-for-one, so that by the time unrealized potential has fallen to zero, the realized potential it has been converted into will be only a tiny fraction, most likely an infinitesimal fraction, of the original, unrealized potential. Consequently, a second transfer would reset the unrealized potential to its original value, which would be realized in new forms and new subtypes of HIV-1, which otherwise would never have existed, some of which may be worse than anything the original transfer would ever produce. Indeed, there is potential for far worse

than anything we have yet seen, as my arguments later on will show.

And indeed, in connection with these later arguments, we will see that in fact there is a third reason, comparable in importance to these two, why new transfers are to be avoided at all costs.

It is sobering, then, to reflect that one laboratory worker is known to have contracted an SIV from sooty mangabeys while handling the virus, and two others have developed antibodies after needlestick accidents, which however may be abortive infections as no virus has been detectable and the antibodies have declined over time (Sotir et al., 1997). Since testing has been far from complete, there may in fact be other cases we know nothing about. No special precautions are being taken to keep this new strain (or strains) of virus from starting a new human epidemic (or epidemics), which, as argued above, might be far worse than existing forms of HIV-2, and indeed, might be worse than existing forms of HIV-1. According to orthodox medicine, the tens of millions of group M HIV-1 cases all arose from a single infection occurring around 1931 (Korber et al, 2000). On what grounds, then, do they conclude this human SIV case, or these cases, will not kill comparable numbers over the next 80 years? No doubt the chances are fairly small, but on what grounds do they conclude they are so small as to make risking tens or hundreds of millions of lives acceptable? This requires a very, very, very small risk indeed, which is clearly not achievable, while in fact no assessment of the risk has even been carried out. The fact is, they strongly appear not even to be aware of the danger.

8.5. A danger from alternative medicine

While mainstream medicine has done a lot in recent years to increase the safety of its vaccines, alternative medicine still presents a large danger through "cellular therapy" treatments involving injections of fetal sheep cells and similar risky preparations (American Cancer Society, 1991). What will happen if a person suffering from AIDS decides such treatments are just the thing to cure him, and the sheep cells injected are infected with the maedi lentivirus? Probably nothing, if it is a single case. If it happens a thousand times, then the result is anybody's guess, but anybody who says the risk is small is talking through his hat. It may be small; it may be large; it may be somewhere in between: there is no possible way to know without doing the experiment. I would recommend against it.

8.6. What still remains

At the beginning of Section 8, I speculated that there were other assaults on the species immune system that I had failed to uncover. Within a mere six weeks of publishing the first version of this paper (on 5 September 2009) I had learned of three more. They necessitated a new version and are discussed below.

In view of this large and quick addition, it seems fairly safe to conclude there are still other significant assaults that I have missed that others may know about. But beyond these, there are likely to be others that no one has thought of and that we won't ever become aware

of unless and until they result in the transfer of a significant new disease. And quite possibly, not even then.

8.6.1. Do-it-yourself bioengineering

The first of these three new assaults is do-it-yourself bioengineering.

Recombinant DNA technology, once requiring an investment of hundreds of thousands of U.S. dollars, has now become very cheap. Outmoded, previous-generation equipment, still highly usable but no longer readily saleable, can be had for pennies on the dollar, or even fractions of a penny, on outlets such as eBay. Interested amateurs are acquiring such equipment and performing their own recombinant DNA experiments in their own kitchens. Ready-made kits capable of transferring genes between species can be bought online for under $300. Within another decade the technology will likely have advanced much further, allowing much more to be done by many more members of the general public. There are websites, such as DIYbio.org, that promote the practice and help neophytes get started. They hope that, freed from the fetters of corporations and institutions, gifted or lucky amateurs may make important new discoveries. (Wohlsen, 2008; Specter, 2009; Anonymous, 2009; Whalen, 2009)

But not all amateurs are gifted, and not all gifted amateurs are lucky. Nor are all gifted and lucky amateurs good. And even the good ones will disagree on what is good and what is bad. And what is good for one person or group is very frequently bad for another. What is good in the short term is very frequently bad in the long term. New lifeforms that escape (but how could they possibly escape?) and are able to survive will evolve and adapt and change in unpredictable ways. A hay-fever sufferer who decides to construct a bacterium that will kill every ragweed plant in the world may, if successful, help hay fever sufferers, but what other consequences would flow from a world without ragweed? What other species may be dependent on ragweed for their survival, and what will their absence mean for the world? What if the ragweed bacterium also kills related plants? Even if it cannot infect them to begin with, who is to say what it may adapt to do in 10 or 100 or 1000 years of evolution? What if the gene for the particular toxin that was meant to kill the ragweed transfers to a bacterium that now harmlessly infects fir trees? What if the final cure for HIV, or some other deadly disease or onerous condition, could have been made from ragweed, but was never discovered because ragweed went extinct?

Perhaps a good-hearted kitchen experimenter develops an *E. coli* that will produce vitamin D, a vitamin much of the world is frankly deficient in and for which many doctors believe the current recommended amounts are much too low. But too much vitamin D is seriously toxic and may be fatal. What if the new *E. coli* produces more than intended in certain people? What if it evolves over time to produce much more than the original version, if the variants arising over time that produce the most vitamin D have some unforeseeable selective advantage and outcompete the rest? A 20-fold vitamin D increase might well be into the toxic zone, and a 200-fold increase almost surely would be. Even a 200-fold increase can happen in just a few years, yet the new microbe may have decades, centuries, millennia to accomplish it, or to accomplish whatever other new and possibly harmful changes improve its ability to compete against a now-changed background of other *E. coli*, and a changed background of other intestinal bacteria, which will arise in response

to the changed environment they now find themselves in. Maybe the *E. coli* will always be of benefit, but one of the changes it occasions in some other organism will be harmful or disastrous. Maybe the vitamin D gene will get transferred to some other resident of the human colon which produces more vitamin D than *E. coli*, either because each cell produces more or because the other resident is more plentiful. Maybe the gene will get transferred to a microbe that exists outside in the ecosystem, with unforeseeable consequences. Maybe one of these organisms will find it has a selective advantage over its kin when it produces an altered form of vitamin D, and maybe this altered form will be harmful to humans or to the environment.

There are bacteria that get into the upper atmosphere and constitute nuclei for ice crystals to form on. Ice nucleation is a crucial step in a cloud's production of rain, but the extent to which bacterial nuclei contribute is unknown. In any event, some bacteria are much better at this than others. Suppose a gifted and lucky amateur develops a bacterium that is superior to anything found in nature? The hope may be to bring more rain to dry areas, but it may also bring more rain to wet areas. And it will likely have other far-reaching consequences. When these new ice-forming bacteria infect plants, they will make them more susceptible to frost damage. The very reason the best of them is so good is that it is a plant bacterium that can feed on its host much more easily if the spots where it has colonized become frost damaged. It has evolved this very adaptation in order to damage the plants it lives on. A better version will presumably result in more frost damage; and even if more rain is in fact a good thing, more frost damage is likely not to be. And modifying the global weather, and the global potential for frost damage, with no possibility of recalling the bacterium if the unintended consequences should turn out to be disastrous, should give even the most reckless reason to pause. (Christner, 2009; Gurian-Sherman and Lindow, 1993; Skirvin et al., 2000)

And all this is presuming the amateurs are good-hearted, social-minded people. There are many gifted and lucky and unscrupulous people in the world. What about those who decide to get rich quick by making a killer virus and extorting millions of dollars from their government not to release it? Or not to give it to enemy governments? Or who hope to sell it to their government's biowarfare program? Or to the highest bidder? And suppose it escapes from their kitchens? Or suppose they are terrorists who frankly intend to use it themselves? Or threaten to use it? Or suppose they are simply not sane, like the religious cult in Japan some years ago that released nerve gas in the subways, killing several: what might they have done had they had access to this technology? What might Jim Jones' cult have done?

There are millions of graffiti artists around the world who paint fancy versions of their names on buildings, subways, and everything else, over and over, in order to be noticed by the public or by their peers. It would be a trivial matter to incorporate a version of one's name, or pseudonym, into an organism and release it, just to spread one's name all over the world (and not just until the paint wears off but perhaps for all time) [24]. This may seem harmless enough, but in fact there is no point doing it unless one's new organism will spread; and since the natural type will generally do at least as well as the recombinants, and probably better, this demands greater changes than simply adding the genetic representation of one's name to a non-functional part of the genome. It may not be so easy to accomplish, but I can think of several ways that I suspect would enable a new organism to rapidly spread, and all of them are dangerous. Just creating a more fit version of an organism, by whatever means, is itself fraught with danger. A rare and insignificant organism no one

cares about may become neither rare nor insignificant if its fitness is increased. And those methods that involve changing or adding genes in ways that nature could not accomplish remove natural barriers and open up new vistas for further evolution that may unfold in unexpected and dramatic ways, perhaps quickly or perhaps not until years, decades, or centuries later [25]. It is likely that the overwhelming majority of detrimental changes would not come about quickly but would only emerge much, much later; and when they do, the effects may be so remote from the original cause of the change that the connection is never noticed, not even if the change is dramatic enough that considerable effort to pinpoint the cause is made.

In the Appendix, I give quite a dramatic example of the remote and irreversible and still unfolding consequences of a seemingly-insignificant change that was identified as the cause only decades after the fact: a new human pregnancy test. This was not even a genetic manipulation, and its effect required only a few decades to dramatically manifest itself; yet it would not have been surprising if the connection had never been made. If the manifestation had required a thousand years to become dramatic, and the pregnancy test had not been used for the last 900, the chances of ever finding the cause would have been slim indeed. Next time someone tells you genetic manipulation has been going on for a long time and there have been no adverse changes to date, first tell him that a few decades is an extremely short time; second, ask him how he knows no adverse changes have occurred; and, third, ask him what percentage of the adverse changes he would expect to see in the first year, the first decade, the first century, the first thousand years after the ultimate cause of the change is introduced. These matters are in general not even considered by proponents of genetic manipulation.

There are many thousands of people around the world who have written computer viruses for motives much like those of the graffiti artists, but here with the explicit intent of seeing them spread around the world. What will these very people do when they gain access to this technology? Some of the computer viruses do harm inadvertently, when they prove to have properties their writers did not foresee. But others are deliberately written to be malevolent, to erase whole hard drives, sometimes ruining people's lives. What will *these* computer virus writers do when they gain the power to manipulate real viruses?

Unlike all the other assaults, which acted to transfer existing organisms from other species or other environments into our species, this one actually creates brand new organisms that have never before existed, some of which may find us to be a very good source of food. But this is also unlike the other categories in having its greatest probable consequences not on new diseases that may infect human beings but on other species and other components of the ecosystem. Therefore, it does not neatly and cleanly fit into my categories.

Moreover, the "do-it-yourself" aspect is also only a part of the story. Do-it-yourself bioexperimenters may be the most dangerous – many of them are poorly trained and are working without supervision under circumstances that make escape of any organism they create that can survive in the wild extremely likely. But official, sanctioned, regulated corporate or university or government researchers also represent a considerable danger (MacKenzie, 2004; von Bubnoff, 2005; Weiss, Rick, 2001). The re-creation of the 1918 flu is the greatest bioengineering risk I know of, whether regulated or not (though there are also great potential rewards); but in fact the regulation is shockingly lax, and the risk could be substantially reduced if the regulation were greatly strengthened. These professional bioengineers are able to make far more sophisticated changes than the home experimenters

can manage. And while unintended escape of their creations is far less likely, it will surely happen many times over the years.

Bioengineering is dangerous enough under the best of circumstances. But do-it-yourself bioengineering is a movement that threatens to give great numbers of untrained, ordinary people the power to make large, irreversible changes in the world. This would be unacceptable even if the changes were completely foreseeable and under their control. But the vast majority of the changes will be unintended and could not have been foreseen even by the greatest mind that ever lived, or ever will live, even using the most powerful computers, software, and databases that will ever be developed. No matter how much the human mind or its products develops in the future, we will never be able to predict the weather, on a day-to-day bases, more than at most a few weeks ahead, because there are too many variables all depending on interactions with one another in ways that feed back on themselves and result in infinitesimal, unobservably small, changes leading to completely different outcomes of the system as a whole. The same is true here. It is simply beyond us, and not merely *us*, but beyond all knowing, period.

It is all well and good to say the technology is out of the bag and there is no stopping it. Maybe not, but that is no reason not to stop it as much as we can. It is, in fact, very like the unrecallable microbe whose release may prove disastrous but cannot be undone. In any case, I am not writing about what should or could be done about it but merely to list it as another, and another rapidly growing, assault on our species immune system. It qualifies for that list even in the exceedingly unlikely event (at least in my view) that it does more good than harm.

8.6.2. Bushmeat

Meat from wild jungle animals, hunted or trapped and killed for food, is called bushmeat. This is a very obvious danger, and one I was well aware of. Indeed, the standard explanation for the origin of AIDS is that it was acquired from hunting, butchering, or eating bushmeat, sometime around 1931 (Korber et al., 2000). There are many problems with this explanation, the biggest three being 1) though it is clearly possible, there is no evidence that it actually occurred, 2) in 1931 the level of bushmeat hunting was not a lot greater than it had been for thousands of years, yet HIV never transferred before, and 3) the whole notion is an obvious attempt to avoid the charge that careless vaccine researchers transferred HIV just as they did SV40, an explanation that has been strongly suppressed yet for which there is considerable evidence that it did in fact occur (see note 21).

What I did not know about bushmeat is how tremendously the practice has grown in recent years (with a significant part of this growth being fueled by the first listed decrement, overpopulation). It is now a multibillion dollar a year business. Several billion kilograms of bushmeat are consumed each year in Central Africa alone (Eves et al., 2008). There is also a large amount hunted in East Asia and South America (Greger, 2006, Chapter 8-c, Wild Tastes; Greger, 2007, p. 247). And it is now being exported to secret, illegal markets in major cities around the world, including New York and Paris (Warfield et al., 2009, p. 1134).

Probably more than 1 percent of the bushmeat comes from apes (Eves et al., 2008, p. 333), and a significantly larger fraction from monkeys. These primates, especially, present

a danger of new disease transfer, because of their close relationship to human beings. But the thousands of other animals that are hunted are also a threat. Indeed, the SARS virus may have come from civets that were part of the bushmeat trade (Greger, 2006, Chapter 8-c, Wild Tastes).

Since I am restricting my list to new threats that have emerged within the last 100 years or so, I did not originally list bushmeat. But now that I have belatedly learned of its tremendous recent growth over historic levels, it is clear that bushmeat is another very major recent decrement to our species immune system. There is a great potential for the transfer of new diseases via bushmeat, whether acting alone or with the help of AIDS as a stepping-stone. The majority of both the world's bushmeat eating and the world's AIDS cases occur together in Africa. Bushmeat hunting in Africa may well not have been responsible for the world's first AIDS epidemic, but that does not mean it will not be responsible for the second.

8.6.3. Modern agricultural practices

Though I shall restrict this section mainly to factory farming, in fact it is larger, with, for example, human antibiotics being sprayed on fields to kill the bacteria that may be causing crop diseases (Allen et. al, 2009, p. 1635), foreseeably resulting in the antibiotic resistance of bacteria inhabiting the mice and rats and other animals that may be living in these fields, some of which bacteria may also be potential human pathogens, such as the bubonic plague bacillus, whose treatment of choice is streptomycin, the antibiotic specifically mentioned in Allen et al.

And though a number of recently-developed factory farming practices present a very considerable danger, I do not have room to write about all of them, or even all the major ones. Instead, I refer you to an extremely important, probably historically important, book I discovered only after the original version of this paper had been published. It is called *Bird Flu: A Virus of Our Own Hatching*, by Michael Greger, M.D. (Greger, 2006). Greger is Director of Public Health and Animal Agriculture at The Humane Society of the United States. His 465-page hardcover book, with 91 pages of references, is published by Lantern Books, but it has been made available, in its entirety, free of charge on the internet, at http://birdflubook.com. Moreover, Dr. Greger donates all proceeds from sales of this book, plus his other books, plus his many speaking engagements, to charity. Such generosity is as rare as it is admirable, and I hope some of those who read the free version and have the money to do so will buy a copy or otherwise contribute to his cause. As we are about to see, it may be as much help to humanity as it is to the animals.

Greger also writes about several other practices that would qualify as species immune system decrements; and some of these, such as the trade in exotic pets (Greger, 2006, Chapter 8-f, Pet Peeves), the "wet markets" (Greger, 2006, Chapter 8-c, Wild Tastes), integrated pig-hen-fish farming in China (Greger, 2006, Chapter 10-a, Pandora's Pond), and the feeding of ground up farm animals and even farm animal excrement to other animals, often of other species (Greger, 2006, Chapter 9-d, Offal Truth), might well be as important or more important than some of the lesser items in my list, such as, perhaps, aging, smoking, and global warming. But I do not have time or room to include them and so refer you to his free and freely-available book for details.

What I do intend to write about here is what I regard as Greger's single greatest contribution. The information that follows is entirely due to Greger, and to the many references he cites. It paints bird flu, and the prospect of avoiding it, in an entirely new light. It is what convinced me that an updated version of my piece was absolutely necessary.

Until I found Greger, every single piece I read about bird flu (at any rate every one that had any mention of its origin) painted it as an unfortunate, random, natural occurrence, an abnormally-fatal bird flu utterly unlike the mild or asymptomatic illness that normally exists among wild waterfowl, a freak aberration, coming out of nowhere, that has so far killed about 60 percent of the humans it has infected – a rate in line with typical strains of Ebola. But Greger presents a massive amount of information arguing that in fact we, ourselves, through our modern factory-farming practices, bred this killer virus. We took an ordinary, innocuous bird flu virus and turned it into a killer. We have done this before, on a number of occasions since the start of intensive factory farming of chickens in the 1950s, and it has been happening with greatly increased frequency over the last couple of decades as factory farming has rapidly replaced traditional farming of chickens. What's worse, the same practices that created this killer disease are also adapting it to spread among humans. (Greger, 2006; Greger, 2007)

Here is how it works:

Most chickens today are reared in conditions of crowding so intense by the time they are fully grown that if one of them falls down it is questionable whether the chicken can get up again, the press of surrounding birds being so great (Greger, 2006, Chapter 12-a, Overcrowded). To quote Greger: "In the United States, the overwhelming majority of the 9 billion chickens raised each year are stocked in densities between 10 and 20 birds per square yard" (Greger, 2006, Chapter 9-c, Stomaching Emerging Disease). This crowding produces great stress, and stress has been shown to significantly depress the chicken's immune system (Greger, 2006, Chapter 12-b, Stressful). Efforts to breed for the fastest possible growth (broiler chickens now have about a 45-day lifespan from hatching to slaughter) produce birds deficient in many other ways, including having weakened immune systems on a genetic basis (Greger, 2006, Chapter 12-e, Bred to Be Sick). The ammonia smell from the decaying excrement they are standing in irritates their respiratory tracts, making them more susceptible to infection (Greger, 2006, Chapter 11-b, "In our efforts to streamline..."). The clouds of dust in the crowded enclosures clog up their respiratory clearance mechanisms, adding to the problem (Greger, 2006, Chapter 12-c, Filthy). Finally, several chicken immunodeficiency viruses, epidemically spread due to the crowding and to the other causes of immune deficiency, add yet more immune deficiency (Greger, 2006, Chapter 12-g, Acquired Immunodeficiency Syndromes).

These unimaginably crowded birds with weakened immune systems, and especially with weakened respiratory immunity, provide perfect vessels for breeding killer bird flu strains from the innocuous ones found naturally in waterfowl, as they are passed many times from chicken to chicken. Waterfowl are the only significant natural reservoir of flu, and in them it is spread through the fecal-oral route. But the incredible crowding of immune-deficient birds allows this fecal-oral virus to change into a respiratory virus and to become far more virulent, not only for the chickens but for mammalian species as well (Greger, 2006, Chapter 11-b, "In our efforts to streamline..."; Greger, 2007, p. 273). Ordinary bird flu will seldom kill an infected mouse. The Z+ H5N1 variety kills 100 percent of experimentally infected mice (Greger, 2006, Chapter 3-f, Year of the Rooster).

This change from innocuous to highly pathogenic has been recorded over and over again when various wild flu viruses have infected chickens raised in factory farms (Greger, 2006, Chapter 11-c, Chicken Surprise; Chapter 13-a, Chicken Run; Chapter 13-c, Made in the USA). The change from a gut-dwelling fecal-oral virus to a lung-dwelling respiratory virus, even one of chickens, greatly enhances its ability to live in human lungs and spread through the respiratory route. But chickens are especially problematic because their respiratory systems contain cells with human-like receptors, which waterfowl lack. By the time the duck and goose viruses have adapted to the chickens, they have gone a long way towards adaptation to us (Greger, 2006, Chapter 11-c, Chicken Surprise; Greger, 2007).

But though adapted to chickens, the new virus can still infect wild birds, who can keep the virus alive even if it is entirely exterminated from the chickens it arose in, and all the chickens of that country, and who can, perhaps several years later, when conditions are right, then rapidly spread our new creation around the world, even into non-factory-farmed backyard chicken flocks, one of which may infect the human being who passes it on enough times to enable it to become a truly human virus (Greger, 2006, Chapter 20-a, Trojan Duck; Chapter 21-a, "Extreme remedies...").

The chickens are a stepping-stone (Greger uses that very word, too), between waterfowl and humans, allowing a means for a water-borne, fecal-oral flu virus of ducks and geese to become a respiratory virus of humans. Should the current bird flu virus ultimately cause a worldwide human pandemic, the consequences could be far worse than the 1918 catastrophe. (I will attempt to estimate the numbers later.)

I have not been able in these few paragraphs to do justice to Greger's massive amount of evidence. It makes up a significant part of the entire book. I strongly urge you to read it all.

Intensive factory farming only began in the 1950s and has become widespread only in the last few decades. Chickens may be the most dangerous, but other factory-farmed animals present other dangers. One day, probably within your lifetime (though maybe only at the very end of your lifetime), factory farming will likely make a very large change in human history [26].

9. Effects on existing human diseases

At first glance one would think AIDS patients and other immune compromised individuals, or transfusions and other unusual assists to spread of microbes, would have no effect on the character of existing human diseases. After all, most existing diseases have been here for a long time, usually for hundreds or thousands of years, and have surely already adapted as well as they are able to. And surely even the more recent arrivals, since they are existing, surviving diseases, will finish up their adaptation through natural processes of living in humans and spreading to other humans, processes that do not require help from AIDS or anywhere else.

But that is too facile.

There is a quite simple and straightforward mechanism through which transfusions could allow existing human diseases to develop new means of spread. Currently genital herpes is usually spread venereally. The herpes virus does not normally inhabit the blood stream, so that a transfusion from an infected person is unlikely to spread the disease. But

perhaps there are rare exceptions. And when they occur, this may be because of some anomaly in the person infected, or because of an anomaly in the virus itself that makes it more likely to infect the blood than normal herpes strains, or because of a combination, or just because of chance. Virtually all mutants are less fit than the normal type and quickly die out. Assuming that these putative herpes mutants exist at all, we know that they are less fit than the normal type, because if they were more fit they would have already long ago supplanted the normal type, and bloodstream infections would be the norm.

But transfusion can allow these less fit mutants to survive. They may be less able to spread venereally, but they can still survive through being transfused into new hosts. (So, in fact, they are less fit under the old conditions but may actually be more fit under the new conditions, which include transfusion.) Whereas previously such mutants quickly died out, now they can survive, perhaps indefinitely, with the assistance of transfusion. They will have time to improve their adaptation to this new environment they find themselves in. They can grow to higher titers and begin to spread through smaller and smaller exchanges of blood. Perhaps they will eventually be able to spread through reuse of nonsterile needles. A new means of transmission has evolved, and the mutant will survive, and continue to adapt, even if transfusions start being screened for herpes, even if transfusions cease altogether.

By artificially preserving what would otherwise die out, transfusion removes the relentless selection pressure on genital herpes that prevents it from evolving. The best-adapted herpes strain has already been found. All the tiny mutations that occur in every infection are less fit and are squeezed out by the normal variety in the struggle for existence, the struggle to spread to 1.0 further hosts, which the normal strain can just barely manage, and which the mutant strains cannot [27].

9.1. The evolutionary landscape

The well-known metaphor of an evolutionary landscape is useful here (Hardin, 1959, Chapter 12, esp. Fig. 12-9, p. 288). Picture a varied topography of many hills and valleys. Some hills are minor; other are veritable mountains. Some valleys are shallow; others are vast chasms. The landscape is in fact a graph. Each possible genetic combination, each possible mutation, of each possible lifeform, whether it ever existed or not, is represented by a point on the landscape. And the elevation of that point represents that genome's fitness. The tops of the hills are the evolutionary peaks. If we take one of the organisms that is halfway up its peak, it will be quickly crowded out by its fitter relative at the top. But if there is no relative at the top, if this is a hill that was previously uninhabited, there is nothing to outcompete it, and, assuming it is able to survive in the absence of competition, it will slowly put out variations in all directions. It will outcompete all variations that are lower down. But it will be outcompeted by its offspring that are higher up the hill, closer to the peak. Therefore, it (or rather its evolving descendant) will inexorably inch its way upward until it has reached the top.

But suppose it has reached the top of just a small hill. Yet right beside it is a gigantic mountain of fitness, far, far better indeed. Even if the mountain is completely uninhabited, the organism is stuck. It cannot evolve its way down its small hill in order to cross over onto the gigantic mountain so close by. It cannot go downward, because its kindred who do

not go downward will stop it in its tracks. It can only go upward.

Of course, it may go a little bit downward for a few generations before its fitter relatives eliminate it. If there is any way to get onto the upward slope of the big mountain with no more than a slight downward detour, the organism may well eventually make it. But all sizable valleys are uncrossable.

Under circumstances when competition is relaxed, because of a sudden improvement in conditions, such as infection of a virgin population, or because transfusion or some other new means allows a respite, it is as if there is a flattening out of the landscape, so that the slopes are less steep and the valleys more shallow [28]. The relaxed competition means that mutants can travel downward for a longer time before they are eliminated. Some that could not previously cross a deep valley, may now be able to cross its shallower incarnation. And once the valley is crossed, and the successful traversers have climbed far enough up the other side to be a self-sustaining population, the deed is done. The new peak will be climbed, even if conditions later become as harsh as ever. At least this is so if the new peak was uninhabited.

With one possible exception, my feeling is that this effect on existing human diseases will be quite minor in comparison with the ravages new human diseases are apt to cause. But it is easy to see that this is not necessarily so. Perhaps there is an existing disease that is on one of these small hills at the foot or partway up the side of a gigantic uninhabited mountain, and perhaps transfusion or some other means allows it to attain the behemoth so near that was always before unreachable. There is no way to foresee what might happen. It could be a world-altering event. And in most cases there is no way to know whether or not there is a mountain close by or whether this local peak is the highest one for miles around.

9.2. The nearby mountain

But there is that one possible exception:

Just as transfusions might both allow the establishment of entirely new diseases and allow existing diseases to develop new means of spread, or perhaps other evolutionary potentialities that could not otherwise be realized, so also AIDS may have an effect on existing diseases, in addition to allowing brand new diseases into our species.

Suppose a disease normally spreads venereally but occasionally produces a mild cough that expels a few germs into the air. Because of its highly specialized mode of transmission, expecting to take hold in quite different tissues, it will be unlikely to cause an infection among those breathing in the germs, especially since the numbers of germs are likely to be much smaller than is the usual case for a disease that specializes in airborne spread, where selection for highest rate of airborne germ expulsion may have been going on for millennia. But if the person who breathes in these germs happens to be an AIDS patient with a seriously weakened immune system, it is possible the infection might take hold despite these obstacles. And if there are many other similarly-debilitated AIDS patients nearby, it is possible the first patient may pass it through the air to a second, and so on.

With each airborne passage the microbe will improve its facility for airborne spread, increasing its ability to take root in this foreign tissue, increasing the numbers of microbes that are coughed out, and increasing the length of time that expelled microbes can survive outside the body. (Even though mere seconds may go by from the time a microbe is

coughed out by one person until it is breathed in by the next, it is nevertheless true that in normal venereal spread the microbe is not outside a body for even an instant, let alone exposed to 20 percent oxygen in a tiny droplet that will rapidly dry out.)

Ultimately, the microbe may become able to infect normal individuals through the air, and a new method of spread will have arisen. Because of the necessity of specialization, it is likely that eventually the microbe will split into two different forms, one of which spreads venereally and the other through the air. This is especially true in this hypothetical case, since the requirements for venereal and airborne spread are so very different. The symptoms also may be very different, so that in fact we now have two very different diseases, even though the causative organisms are still closely related.

Can I perhaps provide an actual example of a disease which might undergo such a transformation? I can indeed, and it is a matter of considerable concern. The disease is AIDS itself.

Being a new disease with only a few-decades-long sojourn in the human race, AIDS, or rather its causative organism HIV, is still improving its ability to grow and spread in this new environment. The most transmissible variants will, simply by definition, be the ones that are disproportionately transmitted. Thus, HIV will inevitably become more transmissible as it adapts, and it may develop new means of spread as it does so, just in the ordinary course of evolution, without having to invoke this new mechanism [29].

I said above that in this particular case there is a very large uninhabited mountain close by. The way we know this is by examining a similar mountain that is plain to see because it is inhabited.

HIV, and the related SIVs of simians, are members of a very unusual group of viruses called the lentiviruses, a small branch of the much larger family of retroviruses. Before the discovery of HIV, only a handful of lentiviruses were known to exist, the best studied being the maedi virus of sheep.

The importation of 20 German sheep into Iceland in 1933 (removing the geographic gap) started epidemics of three different infectious diseases never before seen in Iceland. This was despite very thorough veterinary examinations and two-month quarantines of the 20 sheep, for Iceland had had bad experience in the past with diseases from imported sheep. But the three new diseases were all slow infections, taking sometimes years before the first symptoms manifested; moreover, the German sheep were resistant due to their long history with these diseases. The 20 sheep seemed healthy both at the beginning and the end of their quarantine.

One of the diseases, paratuberculosis or Johne's disease, was caused by a bacterium. Another, a fatal lung disease called Jaagziekte or infectious adenomatosis, was later found to be caused by a retrovirus, but not a lentivirus. The worst of the three, by far, was the lentivirus maedi, which in Icelandic means dyspnea.

Three landmark articles by Björn Sigurdsson in the *British Veterinary Journal* for 1954 describe these diseases, the circumstances leading to their appearance, and efforts to control them, as well as a fourth disease, Rida, that was not new and is probably identical to scrapie (Sigurdsson, 1954a, 1954b, 1954c). In these articles Sigurdsson coined the term "slow virus" or "slow infection" and described the remarkable characteristics of this new infection type. Maedi was the prototype slow virus disease. Its classification, lentivirus, did not previously exist. The Latin prefix "lenti" means "slow."

Maedi is a lung disease, and in the Icelandic sheep, long isolated from other sheep and with no previous exposure to maedi, it was 100 percent fatal. It generally took at least two

years after infection, sometimes much longer, before the first symptoms developed, and then several more months to kill the animal. Symptoms were of a peculiar lymphoid interstitial pneumonia. As is to be expected of a lung disease, transmission was through the air (and to a lesser extent through mother's milk), and occurred largely during the wintertime when the sheep were housed in close quarters inside sheds to protect them from the extreme cold (Pálsson, 1976; Thormar, 2005; Peterhans et al., 2004).

No treatments made any difference. Other methods of control were tried, beginning with slaughtering all symptomatic sheep. The disease continued to spread, often killing 20 to 30 percent of sheep in infected flocks each year. They then tried slaughtering all sheep, symptomatic or not, in flocks that were infected. It continued to spread. They tried building long fences, well maintained and patrolled, separating the parts of the country that were infected from those to which the disease had not yet reached. This also failed. In desperation, about to lose the chief industry of the island, they slaughtered all sheep in the approximately one half of the country that was then affected, even flocks where no sheep had ever come down with the disease. Sheep from the uninfected half were used to repopulate the slaughter zone. This worked, but not without difficulties. The program was completed, or so they thought, in 1952. But several years later, more cases erupted. This time it was only on isolated farms requiring only localized slaughter. The last maedi-infected sheep was not killed until 1965 (Pálsson, 1976).

Shortly after maedi appeared, while it was still raging, a fourth new disease emerged. It bore many similarities to maedi and was also 100 percent fatal. The main difference was that it did not kill through pneumonia but through brain destruction. It was called visna, and turned out to be a variant strain of maedi which had specialized in infecting the nervous system. (Maedi was always the predominant disease, but visna was easier to grow in culture and so has been better studied.) In Icelandic, visna means "wasting."

Maedi (also called maedi-visna or visna-maedi) shows great similarities to AIDS. There are two chief differences. AIDS is not airborne, and maedi produces only slight immune system dysfunction. As for the similarities: both are lentiviruses, both infect macrophages, both are readily transmitted through mother's milk and colostrum, no vaccine has succeeded against either one, despite prolonged serious attempts, both produce an initial, short-lasting infection that seems to disappear, only to reemerge years later in a slowly-worsening form that is ultimately fatal. Moreover, though HIV generally kills through destruction of the immune system, it frequently attacks the brain and may even kill in this manner before the immune dysfunction becomes acute. The brain destruction of HIV bears great similarities to that of visna (Thormar, 2005; Pétursson et al, 1991; Georgsson et al., 1990). Moreover, the lungs are full of macrophages, called alveolar macrophages, which HIV infects. The pneumonia of HIV is not always pneumocystis pneumonia or another opportunistic infection. It can be caused by direct infection of the lungs by HIV itself, and it can be fatal even before marked symptoms of immune deficiency develop. The cause of death is a peculiar lymphoid interstitial pneumonia strikingly similar to that of maedi (Lairmore et al., 1986; Thormar, 2005; Pétursson et al., 1991; Georgsson et al., 1990). This is rare in adults but fairly common in infants infected with HIV (Saldana et al., 1983; Scott et al., 1984).

It appears, therefore, that HIV may be dangerously close to developing an airborne strain, even without considering the role of an immunodeficient substrate in which it can evolve.

9.2.1. Are AIDS patients in fact hypersusceptible targets?

Now in attempting to fit HIV into our model of a pathogen that may develop new potentialities through continued practice in the especially-hospitable medium of immune deficient subjects, we run into an immediate obstacle: Are the immune-deficient subjects in fact an especially-hospitable medium? They may obviously be so for most infectious diseases and most causes of immune deficiency, but are immune-deficient AIDS patients an especially hospitable medium for variant strains of HIV itself? After all, there are large amounts of antibodies against HIV produced, and while these do not suffice to clear the infection from the body, they must have some effect. Moreover, in advanced AIDS cases, where the immune system is weakest and might present the least resistance to lung infection by an incipient airborne strain, CD4-positive T lymphocytes, HIV's favorite target, are seriously depleted, thus depriving the new strain of a potential supply of food.

As for the antibodies, the picture is not so clear. HIV antibodies in some patients neutralize some HIV strains but may have no effect against others. Indeed, they may actually help certain other HIV strains, at least in the test tube [30].

The picture is likewise unclear so far as the number of CD4-positive T lymphocytes is concerned. Late in infection they are depleted in the lung as elsewhere, but for most of the long course of an HIV infection, even though the numbers may be slowly falling in the rest of the body, an excess of lymphocytes of all kinds in the lungs, caused by the HIV infection, results in CD4 T lymphocyte numbers not falling in the lungs; indeed they may even rise a little (Buhl et al., 1993, see p. 1022).

But this is only one part of the story. When HIV infection first begins in a human body, it is usually the macrophages, rather than the lymphocytes, that are the target of HIV infection. And unlike CD4 lymphocytes, macrophages are not killed by the virus. Later in the course of the disease, HIV begins to prefer lymphocytes over macrophages, and the lymphocytes are quickly killed once they become infected. As the number of CD4-positive T lymphocytes falls, immunodeficiency becomes more and more severe, with eventual fatal consequences. But the macrophages remain numerous to the end (Collman et al., 2003; Cassol et al., 2006). And, importantly, even though elsewhere in the body the virus has changed to prefer T-lymphocytes, this does not happen within the lungs. Specifically within the lungs, HIV retains its preference for macrophages (Singh et al., 1999). Not only is its preferred food source not depleted, but the tendency that occurs elsewhere in the body toward the evolution of lymphocyte-preferring strains that do not spread as well, is absent from the lungs.

And indeed, within the lungs, the number of alveolar macrophages is abnormally large, larger than in noninfected people, and this increase begins early in the course of the illness, well before any opportunistic infections arise, and continues even in the late stages of infection. Moreover, the macrophages are in a state of activation, which causes them to develop increased amounts of CD4 on their cell surfaces, making them more susceptible to HIV infection. The activated state also causes them to produce increased amounts of inflammatory cytokines, which makes them still more susceptible to HIV infection. In addition, these activated macrophages and their cytokines activate other immune cells, such as CD4 T lymphocytes, increasing their susceptibility to HIV infection, and rendering even CD8 lymphocytes susceptible to HIV infection (Agostini et al., 1995; Swigris et al., 2002).

In short, HIV sets up especially favorable conditions for its multiplication within the lung, and it would seem that the lungs of HIV-infected individuals are therefore likely to be

especially easily infected by HIV virions coughed out by other HIV-infected individuals, and that this is so even before the immunodeficiency becomes significant, and may well be even more so in the final stages of immune deficiency [31].

Indeed, the circumstances of HIV's colonization and transformation of the lungs are so striking that it is hard to believe that this is not an airborne infection in simians. I have not heard any suggestions along these lines, with most reports assuming sexual spread; but different SIVs in different simians are very different, and I wonder how carefully this question has been investigated in the SIV that became HIV-1, which was one of an unknown number of chimpanzee SIVs. If it is not spread through the air among chimpanzees, then the only plausible alternative explanation I can think of is that airborne spread in an ancestor of the chimpanzee virus is still current enough to cause these changes. In either case, whether the disease is today airborne in chimpanzees or whether a recent ancestor of that virus was airborne, it would seem to be close to achieving airborne spread in humans. For several different reasons, such as *far* greater numbers of *far* more crowded humans, living indoors, often in terrible poverty and infected with other lung diseases, such as TB, or in the case of AIDS, PCP, that produce coughing and that further activate HIV target cells, making them still more susceptible to infection by HIV, and that increase the numbers of these target cells as well, humans are a much better subject for airborne spread than are simians. At the very least there is high potential for HIV to become airborne in the future, as the density of HIV-infected humans grows ever greater, exposing ever-greater numbers of apparently hyperinfectable lungs to ever-greater doses of ever-better-adapted virus.

The ideas near the beginning of this paper whose importance I so greatly stressed, about the numbers of offspring organisms arising from each parent, are again relevant here: Perhaps in the normal lung, an occasional breathed-in virus particle that succeeds in infecting a macrophage does not encounter conditions where the original infected cell infects more than one further cell. If it infects only half a cell, on average, then the infection will die out after infecting just a couple of cells, and no one will ever know that it happened. But when the density of both alveolar macrophages and lymphocytes is increased in HIV-infected lungs, and they are activated as well, the transmission rate will presumably rise, perhaps to exceed 1.0 in the most extreme cases. A seemingly-modest change in conditions, if it suffices to carry the multiplier of transmission from below 1.0 to above, can make a life-or-death difference in the course of the new infection, the difference between infecting one or two further cells and infecting billions. Depending on what infection we are talking about, that may make a life-or-death difference in the individual infected. And if we are talking about airborne AIDS, even if it does not represent a life-or-death difference for our species, it will be extraordinarily large. Even if airborne HIV infections are extremely rare, if they occur at all, then selection for airborne spread is actively underway and it is likely just a matter of time before it is accomplished.

But even if it should turn out for some unanticipated reason that lungs of AIDS patients do not provide an especially hospitable environment for superinfection with other HIV-1 strains, we must not forget about HIV-2. Dual infections with HIV-1 and HIV-2 are very common in the areas of the world where HIV-2 is prevalent (Holmgren et al., 2003; Gottlieb et al., 2003). Either virus could develop airborne or other new methods of spread through practice in individuals rendered immune deficient by the other. Indeed, since in the huge numbers of HIV-1 victims, HIV-2 has a much larger pool of possibly hypersusceptible individuals to practice on, HIV-2 may have at least as much potential for

developing airborne spread as HIV-1.

If it should turn out that HIV-1 and HIV-2 are still too closely related for either to present an especially-hospitable environment for the other, we may one day be faced with other immunodeficiency viruses that are much less closely related, such as the type D simian retroviruses (not lentiviruses at all) that caused severe epidemics of fatal immunodeficiency in monkeys in primate colonies in the 1970s and '80s (Gardner, 1996). I expressed worry earlier in this paper about these viruses (see note 8), because if AIDS provides the bridge that allows them into our species, they might in turn allow in other diseases that AIDS would not. But the possibility that they might allow HIV-1 and/or HIV-2 to develop airborne or other methods of casual spread, turning the entire human race into a risk group, or that HIV might allow the type D viruses to become airborne, may be an even greater danger.

There have been unconfirmed claims of type D simian retroviruses in children with Burkitt's lymphoma and two cases of antibody positivity to type D viruses among workers exposed to primate bites and secretions, from neither of whom could a virus be isolated or detected with PCR. These could both have been lingering evidence of abortive infections. (One is claimed to be an ongoing infection on the basis that the person's antibodies have remained high; but when that person is a primate handler who may get a "booster shot" of exposure to this virus every few years, I think this remains unproven.) To my knowledge, a type D simian retrovirus has only once been found definitely to be infecting a human being. That person, who had multiple evidences of infection and from whom a type D virus was actually isolated, was an AIDS patient infected with HIV-1 (Bohannon et al., 1991; Lerche et al., 2001, p. 1784).

Even if there were no HIV-2, and even if the several different transfers of different varieties of HIV-1 had not taken place, the rapidly increasing diversity of the principal type of HIV-1 may well ultimately lead to forms diverse enough to be able to capitalize on victims infected by the more distant variants. There is a large and growing pool of especially susceptible victims, perhaps protected by antibodies or some other anomaly from easy exploitation. The myriad HIV-1 varieties would be constantly probing these defenses, looking for a way past them. Given their increasing numbers, their adaptability, the growing diversity of both the variants infecting the susceptibles and the variants trying to exploit the immune deficiency produced by the other variants (both categories of which are in fact the very same variants), and given the likely long time horizon before HIV-1 can even conceivably be brought under control, the potential for evolving new methods of spread, with airborne spread unfortunately being among the most likely, appears very great [32].

For the case of AIDS, it seems clear to me that there is a large, nearby, uninhabited mountain, and that is airborne AIDS. It is not possible to know if AIDS is in the process of scaling that mountain or if it is (or will become) stuck on a hill partway up. And if it is indeed stuck, or becomes stuck, it is not possible to know whether individuals immunosuppressed from differing viruses or from other causes will, as they become more varied and more numerous, ever constitute a bridge across the valley. But I think there is a very large potential, and that this is very clear indeed.

10. A summary of the species immune system decrements

Before turning to the practical matter of a possible bird flu pandemic and how bad it might be, I will briefly list the various decrements to the species immune system that we have been discussing, all of which have occurred, or gotten far worse, just in the last hundred years.

First is the AIDS epidemic which will act as a bridge conducting new microbes into our species. In my estimation this is far and away the largest of the decrements, probably exceeding second place by at least an order of magnitude, and in all likelihood exceeding the sum of all the others combined, even when those that I may have overlooked are included.

The remainder are harder to rank, and are not listed with rank in mind.

Overpopulation, and its attendant greater population density, will allow spread of a new microbe into more secondaries, assisting it in its struggle to achieve 1.0 new infections for every old before its numbers fall to zero. Malnutrition, poverty, squalid living conditions, all worsened by overpopulation, reduce immunity and make infection easier. Overpopulation-caused expansion into new territory increases exposure to novel organisms.

Cigarette smoking and air pollution will increase the amount of coughing in a society, and the additional coughing will aid new respiratory organisms in spreading to new contacts. Moreover, at least for certain of these organisms, lungs damaged by these factors may be easier to infect in the first place. Both smoking and pollution have greatly increased within the past 100 years.

Respiratory infections also increase the amount of coughing in a society, and at least certain of these, in particular HIV, will also make the lungs easier for foreign organisms to invade.

Global warming will change the geographic locations where humans might be exposed to potential new pathogens. New pathogens unable to infect their usual human societies because of resistances evolved over thousands of years of exposure to closely-related human pathogens may be able to infect societies without these resistances.

Similarly, increased travel and increased globalization allow virgin populations to be exposed to potential pathogens that may have been kept out of humanity in past ages through the effect of related human pathogens existing in the home territories of these potential pathogens. Rapid travel also vastly speeds up the rate at which both new and old diseases can spread around the world and makes containment of a localized outbreak far more difficult.

Next come several decrements that are related by being the result of medical techniques, sometimes incorrectly employed, but other times the inescapable result of the technique itself.

The larger number of very old people with very weak immune systems who in past times would have died represents a milder version of the decrement due to AIDS cases. In my view it is far milder, probably by two orders of magnitude or more, but my knowledge of the aging immune system is too meager for my view of the magnitude to count for very much.

There are also other, smaller, categories of people with immune systems damaged as a side effect of medical procedures, chief among them probably cancer victims treated with chemotherapy or radiation that can severely damage immunity, though usually only for a

limited time.

The overuse of antibiotics (as a result of AIDS, of dangerous agricultural techniques, and of simple overprescribing) is lowering one recent medical enhancement to the species immune system; and when the antibiotics kill off the friendly flora that help protect us from infection, they are lowering that particular part of the immune system far below its historic, pre-antibiotic levels, and this lowering would occur even if antibiotics were not being overused and even if their intended targets were not becoming resistant.

Transfusions, which entirely bypass the skin and allow new microbes not yet well enough adapted to be able to spread of their own accord the means to spread and the time to adapt, represent, because of their commonness, a very serious decrement to the immune system of the species.

Vaccines, which when contaminated with unintended microbes, allow thousands or millions to be exposed to animal pathogens that might naturally infect a human being never, or one person in the world per century, or 1000 people in the world per year, thereby give the new pathogen many, many extra attempts to achieve through simple chance the several human-to-human passages likely necessary before it can adapt. One might be inclined to view contaminated vaccines as a medical procedure incorrectly applied, but since detection of previously unknown microbes with 100 percent certainty, or anything close, is not even theoretically possible, this decrement will occur even if there are no careless or otherwise inappropriate uses of the procedure.

Transplantation of body parts from one human being to another, like transfusion bypasses the skin, but unlike transfusion transfers also microbes that may not infect the bloodstream. But there are three far larger differences: 1) the recipient is kept deliberately immune suppressed for the rest of his life. 2) The cells in the transferred organ may survive far longer than the short life-expectancy of blood cells in a body not their own. 3) Transplants are far less common than transfusions.

Xenotransplantation, which does the same thing but with body parts from an animal, is far, far more dangerous. Each individual case in my view is far more dangerous even than AIDS, and the reason I have ranked AIDS as so much larger a decrement to the species immune system is purely due to the small numbers of this incredibly dangerous procedure and the huge numbers of AIDS cases.

Closely related to xenotransplantation, and indeed a form of xenotransplantation, even though it is not normally called that, is the cellular therapy of certain alternative medicine clinics that injects cells, often live cells, from animals into humans. This is also terribly dangerous, but at least the recipients are not deliberately immunosuppressed (though some AIDS patients are trying it in hopes of curing or improving their condition).

Then there are needles. In many poor countries needles are reused without sterilization, sometimes with great frequency. Sometimes this is done by doctors in hospitals, but probably more often, by individual families with their own personal needles used for medical injections. The skin is again bypassed, but the amount of blood transferred is probably several million times less than with transfusion. On the other hand, reuse of unsterilized needles might easily be two orders of magnitude more common than transfusion. Related but worse is reuse of needles by injecting illegal drug users. This is a clear misuse of a medical technology. It is worse because the injecting techniques ("booting") potentially expose users to far more contaminated blood, and because so many of them have AIDS now or will get it in future years, making them easy targets for infection by still-poorly-adapted foreign microbes, and because one common means of

obtaining the money to buy their illegal drugs is through selling their blood.

The new practice of do-it-yourself genetic engineering, done in the kitchen or bedroom by anyone who wants to, threatens to make large, unforeseeable, irreversible changes to the biosphere, and perhaps through changes in rainfall patterns or through extinctions of keystone ecological species, or in other unanticipated ways, even to the geosphere. Some of these changes may involve the inadvertent or deliberate introduction of new human diseases. Officially sanctioned genetic research may also be extraordinarily dangerous, and those conducting the riskier experiments almost by definition do not realize the magnitude of the danger. Indeed, their ignorance of the potential consequences is sometimes stunning.

The vastly increased scale of the bushmeat trade exposes huge numbers of human beings to exotic microbes that otherwise would very seldom get a chance to infect anyone. And a large and growing number of these humans will have AIDS, thus greatly increasing the danger of successful transfer to the general population.

Modern agricultural techniques present a number of different decrements, the worst likely being factory farming, which enables infections that could not ordinarily spread among these animals to pass many times through the crowded and immune-compromised legions, until they have adapted and can spread even in less ideal conditions. Frequently these passages result in a much more pathogenic microbe, and when the microbe is flu and the animals are chickens, the result (perhaps not always, but sometimes) is to change a mild fecal-oral waterfowl virus into a highly-fatal respiratory virus of birds and people.

Finally, the grouping together of similarly-hypersusceptible people, especially in hospital AIDS wards, but also in old-age homes and intensive-care units, as well as the voluntary grouping of those such as illegal drug users, facilitates what may be the most important single step in the adaptation of a new disease to our species, the several-times-repeated passing on of the microbe from one human being to another. Jails are a separate but closely related category of grouping. And army camps and conditions of warfare are believed to have played an important role in the 1918 flu pandemic (Barry, 2004).

The interaction of the various decrements will itself intensify the problem beyond the sum of each one occurring in isolation. The commonness or rarity of the various decrements varies enormously. Extremely common are the elderly, smokers, AIDS victims, reused needle incidents, bushmeat eating, and factory farming. Still common are transfusion recipients, chemotherapy and radiation patients, and, increasingly, transplant recipients. Vaccine recipients are of course extraordinarily common, but numbers receiving contaminated vaccines are unknown. At least in the past, they have numbered millions that we know about and an unknown number that we don't know about because a contaminating organism was never suspected. Thankfully, the most dangerous of all, the xenotransplants, are very uncommon, at least so far.

The interaction may come about when a very dangerous but uncommon procedure such as xenotransplantation transfers a new microbe into a single individual and this new microbe requires help from the more common severe decrements, such as transfusion or AIDS, before it can infect its second victim, which will perhaps get it to the point that a very common but less severe decrement, such as reused injection needles, gets it into its third victim. There aren't enough xenotransplantation patients that one of them is likely to infect another (unless they are housed together in a group). But they get the organism into the first human being, and the less extreme but far more common decrements listed above then act as further stepping-stones to enable a successful cross-species jump.

There are actually two importantly different categories of decrement: those like

xenotransplantation and contaminated vaccines that serve to introduce a foreign microbe but don't do anything to spread it person-to-person; and those like transfusion and reused needles that don't do anything to introduce a foreign organism but serve to ease the early difficult passages of the microbes introduced by the first category (and by rare chance events that have always caused occasional infections of single individuals by foreign microbes). AIDS patients belong in both categories, but that is not the biggest reason they are so dangerous. They are so dangerous because they are so common, and so rapidly becoming still more common.

11. Influenza death estimates

Returning now to the very pressing immediate case of bird flu:

I have seen estimates for numbers of deaths to be expected from a pandemic strain of human bird flu that cover an extraordinarily wide range, from a few million to over one billion. This is not entirely improper, because there are several variables that seriously impact the number of deaths to be expected. If these variables all come out in our favor, the smaller estimates are quite plausible. If they all come out against us, then deaths could exceed a billion by a considerable margin.

Let us first try to come up with some kind of estimate for deaths to be expected if the 1918 flu should strike us today. Considering the risk of escape posed by its recent re-creation, this is not an idle exercise.

11.1. Deaths in 1918

The first careful estimate of the world death toll from the 1918 flu was made in 1927. The number it came up with was 21.5 million (Jordan, 1927). Since then several other studies have produced different results. In nearly every case, the later studies concluded the earlier results had been significantly too low. Indeed, in 1951 the well-known demographer Kingsley Davis gave a figure of 20 million just for India, Pakistan, and what today is Bangladesh (Davis, 1951, p. 41), while a 1986 study placed the toll at 18.5 million for India alone (Mills, 1986). In 1991 Patterson and Pyle studied the question and came up with 30 million as their preferred figure for the worldwide total (Patterson and Pyle, 1991).

The latest study, published in 2002 and building on the work of a 1998 international conference on the history, virology, demography, and geography of the 1918 epidemic, concluded the actual total for the world was probably on the order of 50 million, and indeed might have been as high as 100 million (Johnson and Mueller, 2002). This figure of either 50 or 50-100 million has been used in papers published by *Nature, Science, New England Journal of Medicine,* the CDC, the WHO, and other sources that ought to be authoritative (Taubenberger et al., 2005; von Bubnoff, 2005; Oxford, 2004; Morens et al., 2004; Stevens et al., 2006; Sharp, 2005; Osterholm, 2005a; Taubenberger and Morens, 2006; Goodman et al., 2006). I have not heard anyone take issue with the figure of 50 million, though some have thought their 4-10 million estimate of deaths for China was excessive, since there is

some evidence China may have been unusually lightly affected. On the other hand this is a single study, and there are enough careless errors in their tables (the ones I noticed mostly consisted of listing deaths per hundred in the column labeled deaths per thousand, and thus had no effect on the world total of deaths), and moreover the range of 50-100 million is so large, that I would hope for much further work examining this question. If the 100 million figure is correct, this was the greatest mortality from a single event in world history. If the correct total is 50 million, then it was either first or second, depending or whether the commonly-given 50 million total for all deaths, civilian and military, of World War II was a little more or a little less [33]. But whether it is first (possibly by a wide margin) or a close second, the figure would seem to be of considerable historical importance and worthy of much further research.

In this paper I will use a figure of 50 million, recognizing that it is not as firm as I would like. I am by no means certain that it is not too high, but I think it is not *significantly* too high, while any appreciably lower estimate stands a real risk of being significantly too low.

11.2. Deaths if 1918 flu struck today

11.2.1. World population increase

There have been large changes in the world since 1918, and four of these especially would increase deaths beyond what occurred in the earlier epidemic, if the 1918 flu should strike today. The first change is the huge increase in world population. In 1918, there were a little under 2 billion people in the world. As of June 2011, the U.S. Census Bureau estimated world population at 6.925 billion. The factor of increase is very nearly 3.5. Consequently, all else being equal, we should expect 3.5 times the number of deaths if the 1918 flu struck today.

11.2.2. Population density increase and clustering (urbanization)

But all is not equal. In addition to the greater population, there has also been a large increase in population density. It is not merely that 3.5 times as many people are now living per square mile on the earth's surface. This is because the fraction living in urban environments in 1918 was somewhere on the order of 20 percent [34]. By 2005 it had increased to 49 percent and was projected to pass 50 percent sometime in 2008 (UN Population Division, 2006, p. 9).

It is clear that greater population density implies that a greater proportion of the population will come down with flu. But it is not so easy to know how much greater.

Indeed, if we pick simplified cases that are easy to calculate, greater density will often make no difference at all, because all susceptibles become infected at the lower density. Here are two examples: Imagine a population of 1000, all of whom are initially susceptible,

one of whom becomes infected with a pathogen that can initially spread to 2 further people. In addition, assume that all infected people recover and are immune. If we round off fractional cases to the nearest integer, then cases will run 1, 2, 4, 8, 16, 31 (because now only 969 of the 1000 are still susceptible, and 16 x 2 x .969 = 31.008; we are assuming the pathogen contacts individuals at random, and the fact that only .969 of the population is now susceptible, proportionately reduces the 32 that would be infected), 58, 102, 159, 197, 166, 85, 29, 8, 2, 1, 0. In the end there have been 869 cases and there are still 131 susceptibles that were never infected.

If we increase the density to the point that each case now infects 3 more instead of 2 (assume each case now has 50 percent more contacts capable of spreading the infection, perhaps because density has increased by 50 percent; note, however, that threshold effects, such as transmissions not occurring until distance is less than 1/2 meter, can cause a 50 percent density increase to yield either far more or far less than a 50 percent increase in transmissions), then cases will run 1, 3, 9, 27, 78, 206, 418, 258, 0. The 258 would have been 324 (i.e., 418 x 3 x (1000 - 742 previous cases)/1000), but there were only 258 susceptibles left. Every member of the population has become infected; therefore any further density increase cannot increases cases at all.

In the real world, there are great variations in density. Individuals will also vary greatly in their susceptibility to a new pathogen. Some susceptibles will catch it with ease, while others will require far more intimate exposure. In the real world, greater density will always increase cases, but it is difficult to know by how much.

I am rather arbitrarily assuming that the 3.5-fold greater population density of the world today compared with 1918, together with the 2.5-fold greater fraction of people living in the high-density of urban areas, would increase cases by 5 times the number infected in 1918, instead of just the 3.5 to be expected from the larger population alone. This is a 43 percent increase in cases due to density.

In addition to increasing the number of cases, greater density will speed up the epidemic. In the two examples above, the second not only produced more cases but did so in about half the time of the first example. At its height, 42 percent of the population became infected in just one generation of spread. Almost half the population would have been sick at once, even if we assume all the people infected earlier had fully recovered.

In the first example, the largest generation represented less than 20 percent of the population, and its slower pace would mean that more of those infected in preceding generations would have had time to recover, producing an immune population better able to care for the smaller numbers of the sick. Even if recoveries are so quick that all members of the preceding generations are well by the time the current generation falls ill, the fact that with increasing density each generation is a bigger multiple of the preceding one unfavorably alters the ratio of recovered to sick. Under this quick-recovery assumption, in the first, slower example, at its height, there are 197 ill and 381 who have already recovered and can safely care for them. At the height of the second example, there are 418 ill and only 324 who have recovered.

In our hypothetical examples, the disease was never fatal. But with a disease that is highly fatal, where the seriously ill are too sick to take care of themselves, the fatality rate may vary significantly with whether or not there is anyone available to give assistance. Immune members of the population can also safely continue their normal, perhaps important, positions in society, helping to forestall or to minimize social breakdown. And of course, social breakdown is far more likely if 42 percent of the population are ill at once

as opposed to 20 percent. Therefore, in addition to increasing the number of cases to be expected, greater density will increase the fatality rate, due both to diminished care for those who are ill and to increased social breakdown. I do not know how to estimate these numbers and am adding nothing to the total. This makes the 5.0 estimate given three paragraphs above even more conservative. In the case of social breakdown, especially, there is potential for terrible tragedy. Therefore, I shall consider it in more detail.

11.2.3. Potential for social breakdown

The far greater potential for social breakdown is the fourth large change to the world since 1918 (the other three being greater population, density, and urbanization). Today society is far more intricately organized, and important elements are far more spatially separated. In 1918 workers mostly lived within walking or bicycling distance of their jobs. Food was grown on farms surrounding the major cities. Today there are whole countries that import major portions of their food supply from other countries. There are whole countries that import half or more of their oil from other countries, sometimes thousands of miles away.

After hurricane Katrina, there was a substantial breakdown of society in New Orleans. Many people who survived the hurricane and flood died days later as a result of this social breakdown. And yet, considerable aid flowed into the city, and safe haven was available in cities and towns within the surrounding few hundred miles. In a generalized flu pandemic, few will have safe havens to escape to, and there will be no aid coming in from outside, which will be far too busy coping with its own cases. It will be as if Katrina had struck the whole world, instead of just one city of well under a million people, and the surrounding area, in the richest country in the world. And it will go on for much longer than a few days.

In 1918 there was also a considerable problem of social breakdown, and people also died as a result. I haven't seen estimates of these numbers, but it is reasonably clear that the numbers today would be far greater.

Here is where urbanization may take its greatest toll. City dwellers are much more dependent on a functioning society than are those in the countryside. There is very little food produced within the city. The great bulk of it must be shipped in from elsewhere. If these shipments are interrupted, the shelves of the grocery stores will be empty within a few days.

But it will be extremely hard to keep services operating in an atmosphere of panic and megadeaths. And these very services, if they are maintained, will be one of the vehicles, one of the vectors, via which the epidemic is spread. In order to contain the infection, or slow its spread as much as possible, all transportation into and out of affected areas needs to be suspended. All attempts by city-dwellers to escape to safer haven need to be blocked. If this is successfully done, a great many city dwellers, never infected with the flu, will simply starve to death, or die of thirst or fires when water systems break down and there is no one to repair them, or cold if fuel supplies fail in the wintertime. But if it is not done, then truckers coming and going with supplies or city-dwellers escaping to safer ground, will carry the infection with them, broadening the scope of the tragedy. And within the city itself, workers going about their *essential* jobs will spread the germs around. Workplaces, in fact, are one of the prime locations for spreading infections.

Not only is a much larger fraction of the population urban today, but, at least in the developed world, the fraction of this urban population with recent roots in the countryside is much smaller. Today we may be very competent at running our computers and our microwave ovens, but far fewer of us would be able to fend for ourselves in the absence of a society that was providing us with finished goods in exchange for money.

In a world which is 50 percent urban, all of the food is being produced by half of the population (actually less than half, since many rural-dwellers are not engaged in producing food), and some large fraction, perhaps approaching half the food produced, must be shipped, sometimes over long distances, to the cities which depend on it for their lives. This is a precarious situation, and if a large number of the producers or the transporters fall sick or die, or are unable to obtain the fertilizers, pesticides, fuel, and many other needed supplies, or if they lock themselves in their houses, or are laid off when their transportation companies are unable to function, those remaining will likely not be able to supply enough food to keep all the urban-dwellers alive. In a situation in which some people *have* to die, because there is just not enough food to keep everyone alive, there will likely be great contention for whatever food supplies remain. People are not likely to simply starve to death quietly. And this will result in still more social breakdown and still more deaths.

Water supplies might often require little in the way of maintenance or operation. Purification might be more problematic, but two drops of sodium hypochlorite bleach (e.g., Clorox) after sitting for half an hour, will render a liter of water at least reasonably safe to drink. Electricity might represent a far larger problem. This is a high-tech industry requiring many skilled workers and, except perhaps for hydroelectric plants, a potentially difficult-to-obtain steady source of fuel. The failure of a single key plant can cause cascading problems that shut down large parts of the power grid. If the failure is confined to a single plant, the grid will likely be fixed within at most a few days. But if there are a number of such failures, prompt restoration becomes far less likely. Failure of the power grid is much more than an inconvenience. Nearly all computers in the affected area will fail. Computers are now *necessary* for the operation of all but the smallest businesses and virtually every industry. Until electricity is restored, society will be unable to function [35].

Society is vulnerable in another way. Consider a beehive with its architecturally perfect hexagonal cells, its passive and active ventilation systems that keep the temperature inside nearly constant, its scouts and foragers that find new food sources and inform the hive of their precise locations, its complex division of labor. Or consider an African termite mound, whose physical structure, at least, is even more impressive.

None of the bees or termites have any idea how to build or run such an elaborate and well-adapted enterprise. The structures and the organization come about as a complex interaction among really dumb bees and termites, which somehow have *distributed among them* the knowledge, or at least the ability, to construct these monumental edifices (Hofstadter, 1980, pp. 358-359; Wilson, 1971, Chapter 11, pp. 197-232).

And there are some strong similarities to modern society. Consider a large factory that turns out complex equipment. It runs just fine with nearly everything done by perhaps many hundreds of poorly-educated workers sitting at assembly lines doing the same small job over and over on each item produced. Whether they are making jet engines or computer motherboards, it is likely they understand almost nothing about how the finished product works or the role their particular small task plays. However complex the factory, however complex the product produced, it is likely that it requires very little oversight or intervention from anyone who understands the overall operation of what is going on.

But it is different from the beehive or the termite mound, in that at some point there was a person, or a set of a few people, who did plan and understand its overall workings. The original planners may be long gone, but their successors learned enough at least to keep it going, at least as long as conditions are relatively normal. But this knowledge of how to keep things going in normal times is not the same as how to rebuild the factory should it burn to the ground. And the knowledge of how to rebuild it should it burn to the ground is not the same as how to rebuild it if all of society has ceased to function.

And perhaps the key point is the small number of people who have this knowledge, such as it is, and the likely lack of redundancy. Very probably no one person knows enough to successfully rebuild the factory, but perhaps a dozen of the smartest and highest-level managers with the longest experience and broadest experience might distributed among themselves have the knowledge. But suppose half of these people are dead or have run away with their families to their cabins in the woods? One key missing person may render the repair impossible. And they may well not be paid for the time and effort they invest unless and until they are successful and the enterprise is back up and running and generating income. This may never happen or it may take a considerable while. Many people may feel they should instead be taking steps to secure the immediate safety of their families.

And suppose 90 percent of the factories have managed to assemble sufficiently knowledgeable teams, but before they can get started, or at least before they can finish, they require significant parts of the rest of society to resume functioning. They have to be able to buy fuel and raw materials. There must be a means of selling and distributing their output. Their employees must have some means of getting to work. If employees drive cars, this requires the very complex system of supplying gasoline to the filling stations to be functional. In order for it to be functional, much of the rest of society must be functional. If 10 percent of factories are not able to assemble sufficiently-knowledgeable teams, then it is an open question whether society can rebuild itself, regardless of how good the teams at the other 90 percent of factories are. An important point is exactly which factories would lack the teams. It would likely be the largest and most complex factories that would be disproportionately included. And these might disproportionately be the most important. What if they include many large oil or coal-fired electric plants? What if they include many nuclear plants?

Society grew up organically, a little at a time, with incremental changes, over decades. If it is suddenly rendered nonfunctional and large numbers of its workers die, it is an open question whether, once the epidemic has passed, the remaining knowledge and manpower would enable restarting society in a timely manner. Like a computer attempting to boot, many things have to happen in a highly interrelated way, and a single key failure can sabotage the entire enterprise. A few days' delay might be acceptable. If it takes two months to reassemble society, there will be massive deaths as a result.

Society cannot be rebuilt unless it can get its components up and running. But many of the components depend on a functioning society in order to work. The growing trend toward "just-in-time" manufacturing (where supply systems are so closely coordinated that inventories are nearly non-existent and arriving raw materials go directly onto the production line, eliminating warehousing and thereby saving costs) only makes the problem worse. The larger its inventory, the longer an industry can continue to supply its possibly vital product to the rest of society, even if it can no longer obtain the raw materials to make the product. The inventories of all the vital industries constitute a "rainy day fund" that can

keep society, or parts of it, going for a time, even when vital systems fail.

The just-in-time business model can be thought of as mining social stability for private gain. It cannot exist except in a highly stable social system. Yet the more that businesses turn to just-in-time methods, the less stable the social system becomes. And competition is forcing ever-greater reliance on just-in-time: The advantage gained by a company that converts to just-in-time methods is frequently large enough to force its competition to follow suit or go out of business.

If too much of the stability is mined out of society and converted into just-in-time factories, the system will be prone to large-scale collapse in the event of a serious shock, such as a calamitous pandemic. The lack of inventories increases the likelihood of a breakdown when society is subjected to stress, increases the likely size of any breakdown, and perhaps most profoundly of all, increases the difficulty of restarting the society. It requires a larger portion of society to be up and running before the *vital* parts can be successfully restarted. It makes everything more dependent on the smooth functioning of everything else. Yet in a generalized social breakdown, almost nothing will function smoothly. How is it possible to get from that state back to the pre-breakdown conditions?

For most of 1929 the United States' economy was booming. But on 29 October of that year, there was a stock market crash. Overnight, society had changed and could not be put back together for several years, during which time as many as 25 percent of would-be workers were unable to find employment. Profound changes can happen overnight with little or no warning.

I do not know to what degree social breakdown, perhaps worldwide social breakdown, would manifest itself or how to count the extra deaths that would result. Many will no doubt say I am exaggerating, and for all I know, perhaps I am. I am doing the best I can, but the uncertainties are so great, even in my own mind, that, as I said above, I am not adding anything to my totals, effectively counting them as zero. But at least in those gigantic urban areas like Shanghai and Mexico City and Sao Paulo and New York, it is difficult to see how actual mass starvation could be avoided if a true pandemic strikes. The worst epidemics will be in the very urban areas that are most dependent on supplies and services that their individual members cannot independently provide for themselves. Not even in good times.

Despite these uncertainties, there are a two important points that are clear. 1) The greater the deaths due to flu, the greater will be the social breakdown and the deaths that result from that cause. 2) Social breakdown will feed on itself and lead to greater social breakdown.

It would be useful to know the effect of social breakdown on the spread of the epidemic, but here things are less clear. If regulations, such as quarantine or limiting time outside, would be promulgated and enforced, and if they would have a significant effect on slowing the flu, and if social breakdown prevents or reduces enforcement of these regulations, then social breakdown may worsen the epidemic itself. But to the extent that it makes people even more afraid to go out, or lessens their incentive to go out by shutting down their workplaces, it could act as a kind of quarantine measure of its own and slow the spread of cases. To the extent that it drives even more people to flee the flu-ridden, famine-stricken cities, it will almost certainly speed up the spread of the epidemic (even if it does not increase the ultimate number of cases), resulting in less care and more deaths for patients as the hospitals are more severely overwhelmed and the immune caregivers are fewer.

11.2.4. Medical progress since 1918

In addition to the four negative large-scale changes since 1918, there is one that is potentially positive. That is the great degree of medical progress that has occurred. Unfortunately, at the present moment, medical interventions that would help with flu are quite limited. To the best of my knowledge there is currently no candidate vaccine against the 1918 flu, should it escape from the experimenters. And while several new vaccines against bird flu look promising, they are untested in preventing actual cases of bird flu, and, above all, are in too short supply to make a significant difference in a worldwide pandemic (Wright, 2008). If the world would divert even 1 percent of its annual defense budget toward producing vaccine, certainly at least the supply could be made adequate in short order. The number of lives at risk for lack of vaccine wholly dwarfs all conventional threats that the remaining 99 percent of the defense budget would be directed against.

We do have much better surveillance systems and much faster tests and communications systems now than in 1918. And the remotest areas of the world, where an epidemic might spread beyond any possibility of control before the world even became aware of it, are far smaller. This will not help at all if flu spreads out of control, but it may make it possible to stop a potential epidemic before it ever gets started. But it is likely that this advantage is more than offset by the speed and frequency of travel today as compared with 1918. These will make an incipient epidemic far more difficult to stop.

One might hope that antibiotics would today be able to stop the bacterial pneumonia that frequently follows the flu and that is the biggest killer in most flu epidemics. Many of the 1918 victims died of bacterial pneumonia, but many other deaths were due to flu itself, which was simply far more virulent than anything that has been seen since. But if such an epidemic should occur today, it is questionable how many lives antibiotics will be able to save, simply because the medical system will be so overburdened and so crippled that many people will never see a doctor or nurse. Even those who do may benefit little: supplies of antibiotics may well be exhausted before the epidemic runs its course, and, at least in the United States, mechanical ventilators are barely adequate to handle a normal flu epidemic (Osterholm, 2005a, 2005b). It would be useful for individuals to store up a supply of antibiotics effective against the pneumonia that follows flu; and since there is indeed a good vaccine available against pneumonia, vaccinating much of the general population against this pneumonia might prevent a great many deaths in the event of a flu pandemic.

I have actually not seen any reports of deaths from the sporadic cases of bird flu in humans as being due to bacterial pneumonia; but that is probably because most cases were given antibiotics to prevent it. Otherwise, it is likely the already horrific mortality rate would have been even higher.

And diabetics and others requiring lifesaving drugs should store up a supply. For those needing rare or orphan drugs, it would be good to acquire as large a supply as possible, since it might take a very long time before the more exotic items become available again. These and several other ways in which both societies and individuals can protect themselves are discussed in a 53-page internet article by Axel Goetz, M.D., Ph.D., which also has much other useful information, some of which I saw nowhere else, and is one good place for someone new to the subject to start (Goetz, 2006). There is even more such useful, practical information in the hardback book by Michael Greger, M.D., which he has generously made available for free on the internet (Greger, 2006).

An interesting and potentially extremely important paper by Cannell et al. (2006) makes

a strong case that lower levels of vitamin D in winter months, caused by lack of exposure of skin to the ultraviolet rays of sunlight, accounts for the tendency of flu epidemics to occur during the colder parts of the year. They provide several significant lines of evidence, both theoretical and empirical. A letter to the same journal commenting on their piece adds even more evidence: While investigating whether supplemental vitamin D would help prevent bone loss in post-menopausal black women, Aloia and Li-Ng (2007) noticed a large effect on the number of colds and flu reported by the 208 women studied. The 104 women given placebo reported 30 colds and/or flu episodes over the course of 3 years; the 104 women treated with 800 International Units of vitamin D3 for the first two years reported 8 episodes, and during the third year, when they took 2000 IU per day, only one episode.

These results are quite striking – as good as many vaccines – but other studies have found a much smaller effect. It is possible the effect was so large here because the subjects were black: the same darker skin that blocks UV rays and protects against sunburn also blocks the UV rays the body needs to produce vitamin D, so that dark-skinned people, at least in temperate latitudes where this study was done, are often deficient in vitamin D. On the other hand most other studies have not used enough vitamin D or continued for long enough. Cannell (2007) suggests testing with enough vitamin D to bring blood levels up to those naturally occurring during the summer among people exposed to adequate sunlight. This would require supplementation with 4000-5000 IU per day in the wintertime (Cannell, 2006).

Since those studying vitamin D almost universally agree that the commonly recommended 400 IU is much too low; since vitamin D is safe up to a maximum dose of 10,000 IU per day (Heaney, 2008a); and since there is abundant evidence of D's benefits on bones, the cardiovascular system, the neuromuscular system, and, especially for our purposes here, the immune system (Heaney, 2008b; Cannell, 2006), there would seem to be little or no downside to taking 2000 IU per day, and perhaps as much as 4000 or 5000 IU per day. There is, however, considerable proven upside, together with at least a moderate chance that it will greatly reduce risk from influenza.

The 1918 flu and today's bird flu are very different from regular flu, so it is dangerous to generalize. But Cannell et al. (2006, 2007) point out that vitamin D decreases production of the inflammatory immune factors, whose overstimulation is responsible for much of the excess mortality of both these diseases, while increasing the ability of several other elements of the immune system to combat viruses similar to influenza.

Another thing that could be done now but is not being done, yet might be of great importance, is vaccinating populations in China, Vietnam, Indonesia, and other countries where a new pandemic is most likely to begin, against the common flu for which we do have a proven vaccine. One of the most likely routes through which bird flu might gain the ability to spread readily in humans is by acquiring genes of the human flu from a person who is infected with both human and bird flu at the same time. We can minimize the occurrence of such dual infections through vaccinating the populations at greatest risk of catching bird flu against human flu. Flu vaccine is not expensive, but some of these areas are very poor. The rich world should supply the vaccine to these populations not because of any desire to help the poor but in a desperate attempt to save their own skins. I saw this idea in an article by an economist published, so far as I could tell, only on the internet, while it has been ignored or overlooked both by doctors writing in medical journals and by policymakers (MacKellar, 2005) [36].

It is a sobering fact that many of the advances medicine has made since 1918 that could

be employed to reduce the death and devastation of another killer flu pandemic, would simply go to waste if the pandemic occurred today.

Whatever the reduction in deaths due to medical progress, it seems likely, at least to me, that it would be less than the increase due to social breakdown. Since I did not add anything for the latter, I will not subtract anything for the former. However, a very dramatic reduction might be in order if a successful vaccine could be developed and produced in quantities large enough to protect the entire world before a pandemic occurs.

Under these assumptions, then, of five times the 1918 cases, and 50 million deaths in 1918, and positive and negative effects on the death rate from medical progress and social breakdown canceling each other out, we arrive at an estimate of 250 million deaths if the 1918 flu should strike today.

11.3. Deaths from bird flu

11.3.1. The number infected

Let us turn now to the number of deaths to be expected if, instead of 1918 flu, we are struck by bird flu.

According to various sources, when a pandemic strain of influenza strikes, anywhere from 15 to 50 percent of the world becomes infected (Garrett, 2005, pp. 4, 17; Lewis, 2006, p. 144; Taubenberger and Morens, 2006, p. 15; Goodman et al., 2006, p. 7; Barry, 2004, p. 114). In the 1918 pandemic, up to 50 percent may have fallen ill (Lewis, 2006), though a more common figure is one-third. For purposes of this estimate, I will assume a 30 percent infection rate if bird flu should emerge as a pandemic. With the current (June 2011) world population at 6.925 billion, this represents 2.07 billion people.

11.3.2. The bird flu death rate

Those few who have so far become infected by bird flu have died at an alarmingly high rate of around 60 percent. In contrast, the highest credible figure for 1918 would be about 10 percent of victims dying, and some have estimated the death rate to be as low as 2 percent. The disparity in fact may be much greater, since I am not aware of any bird flu deaths due to bacterial pneumonia, though it is possible some of those who never make it to the hospital are dying in that way (Taubenberger and Morens, 2008; Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus, 2008). The death rate from bird flu all by itself is on the order of 60 percent, while the 10 percent rate of the 1918 flu included deaths from flu and bacterial pneumonia combined; and many have opined that of the two, pneumonia was the bigger killer. This decidedly seems to have been the case in the United States (Taubenberger and Morens, 2008), but may have been less so in underdeveloped areas of the world, with many malnourished people or others whose health was already

marginal, and especially in aboriginal areas with little historical exposure to flu. For many in these areas, the 1918 flu may not have needed the help of pneumonia to finish off its victims.

11.3.2.1. Is it too lethal to spread?

Many authors have proclaimed the seemingly obvious point that before a truly deadly disease can become a pandemic, it must moderate its virulence, lest its victims die before they have a chance to infect further victims. While there is obviously an element of truth to this reasoning, I think it is very far from being the whole story, and in fact that it represents little more than wishful thinking. At the end of this paper I have included a detailed appendix arguing this position. I conclude there that the situation is complex, with evolutionary forces pulling in various directions, and indeed, that in certain cases the most virulent strains may be favored. Sometimes this is just because the strains that grow to the highest titers in the human body are likely to be the ones that spread most readily, and for obvious reasons, these high titers may make their victims especially sick. In this case, virulence is merely an associated trait, and rather than being evolutionarily selected for, what will be selected for are elements that diminish the virulence without diminishing the high titers. This evolution may or may not be significant, depending on how much separation it is possible to insert between these two rather closely-connected traits. In a case of a one-time episode, such as the 1918 flu pandemic, there is also the question of how much can be evolved during the limited time it will exist, and whether a meaningful degree of moderation could be accomplished before the major part of the pandemic has passed.

As to this last, it is possible that the evolution would take place in birds and that the strain that finally gets started in humans would be one that already shows high-titers and low virulence. (A strain that shows low virulence in birds may well show very high virulence in humans. But if many different bird strains exist, those that in fact show the highest titers and lowest virulence when they infect humans, may be more likely to spark a human pandemic.)

But there are also cases where greater virulence will be positively favored, in and of itself, because killing a larger fraction of its victims will actually assist the pathogen in spreading. (See Appendix.)

There are also two very different scenarios for how a bird flu pandemic might arise. It may be a true bird flu or it may recombine with an existing human flu strain to become a hybrid. Most epidemics seem to be of the latter sort, but the 1918 flu apparently came straight from a bird (Tumpey et al., 2005). If the pandemic is caused by a bird-human combination, then its properties might be very different from the current bird flu, and we might hope, with some reason, that it would be much less lethal. However, the current bird flu apparently would not have to modify itself very much in order to become much more contagious in people, and this route may be at least as likely as hybridization. Just one or two amino acid changes will allow bird flu to infect human cells more efficiently (Stevens et al., 2006); and even if this is not enough to permit epidemic spread, it may make person-to-person passages sufficiently more likely that whatever further changes are still required can then take place.

In my view the most likely scenario for a bird flu pandemic, especially if it comes

straight from a bird, is for it to be about as lethal as the cases we have seen already. Even though victims die at a high rate, they do not die so quickly that their infectiousness is seriously compromised. On average, they live 9 days after the first symptoms (WHO, 2007a), and infectiousness may begin a day or two before the first symptoms. In no flu epidemic does infectiousness last more than a few days. Indeed, despite its high mortality, this bird flu appears to have a substantially longer infectious period than the more typical flus, which various estimates have placed at 2 to 5 days (Cauchemez et al., 2004; Fraser et al., 2004).

11.3.2.2. Points against the dire prospect

I can think of two significant points that can be made against this dire prospect.

1) Since very few people exposed to bird flu from birds ever become infected, it may be that those who do are genetically or immunologically especially susceptible. If this is so, we cannot extrapolate the outcomes in those cases to the rest of the population, who are different and who may well be more resistant.

I do not know how significant this point is. Against it is the fact that in the several known clusters of cases the mortality has also been extremely high, though similarity in the genetic background in family clusters and in the environmental background in others, might partially account for this. So far, in family clusters of cases, it seems to be mainly the blood relatives who are infected. (I have several times seen the claim made that it is *only* blood relatives who are infected. However, this seems untrue. See, e.g., Olsen et al. (2005), where for cluster 11 not only were a man, his sister, and grandfather infected, but apparently also two nurses who cared for the man. They were later hospitalized with severe pneumonia, and one of them tested positive for bird flu. Since bird flu is not so easy to test for, I suspect they both had it. Their table of family clusters also shows three wives, and while it is possible the wives and husbands were blood relatives, it seems unlikely to me that this would have been true in all three cases.)

It has been speculated that the target cells of bird flu, which are ordinarily further down in the lungs than the target cells for human flu, making them harder for the virus to reach, may be more plentiful higher up in the respiratory tract in certain families (Webster and Govorkova, 2006). This would explain their greater susceptibility, but it is not clear to me that it would cause any increase in severity. Rather (just as in the case of AIDS) these families, if they exist, represent a path through which a virus ill-adapted for human spread among the majority of us can travel until its adaptation has improved, through transit in these easy targets.

Contrary to this speculation, a recent paper (Pitzer et al., 2007) performs a statistical analysis and concludes that the incidence of blood-relative infections is in fact no greater than would be expected in the absence of any familial genetic susceptibility.

My guess is that chance factors, rather than greater susceptibility, explain most of the infections to date, and if I am wrong I still do not see any reason to lower the mortality rate. When AIDS cases start becoming infected, their mortality will likely be significantly different, and at that point differing susceptibility will need to be taken into account in estimating mortality rates.

I am quite aware that I could be wrong in not reducing the expected mortality on this

basis, but this is the best guess that I can make. If this is an error, it is a potentially highly significant one, so that further evidence on this point is urgently needed.

2) The lethality of the cases that have occurred already may be much less than the lethality of the cases that have been counted. The only cumulative record of cases I am aware of is kept by the WHO, and it is hard to know how to interpret it. To begin with, many cases are missed. It is reasonable to suppose that a much higher percentage of the mild cases are missed than of the severe or fatal ones. Indeed, even some of the deaths are being missed. The 8-member family cluster in Indonesia was started by a woman who died and was buried without bird flu ever being suspected. She is now assumed to have had it, only because 7 of her relatives came down with bird flu shortly thereafter (and 6 of them died). If they had not become infected, her death would have passed unsuspected. And even though epidemiologists, including those at WHO, now consider her to be the index case of the cluster (WHO, 2006a), she has still not been counted among the statistics, because the list is restricted to "laboratory-confirmed cases."

Of three members of another Indonesian family, two children and their 38-year-old father, who died within days of each other with similar symptoms, only the father's death was initially counted in the statistics. It took over a year before limited samples from the dead children confirmed one of them as a bird flu victim. The death of the second child has still not been proven to be due to bird flu, so that this case still does not appear in the WHO tabulation of laboratory-confirmed cases, despite the virtual certainty that she was also a victim (WHO, 2006e; WHO, 2005).

In a third Indonesian village, two young men, cousins, fell ill with similar symptoms on the same day. One died and one recovered. The illness of the one who recovered was shown to be due to bird flu. No samples were available from the one who died. A 9-year-old girl from the same village died of bird flu 10 days after the young man, as did a 35-year-old woman two days later. The cousin's death is strongly suspected to have been due to bird flu, but again it is not being counted (WHO, 2006c; WHO, 2006d). Moreover, an unspecified number of other deaths from respiratory illness occurred within a few days of these cases, but no samples were taken. These deaths are also not being counted, even though "some of these undiagnosed deaths occurred in family members of confirmed cases." The total population of the three hamlets of the village where all these deaths occurred within at most a few weeks was only 600-1200 (WHO, 2006d).

In a fourth Indonesian village, a 7-year-old girl died of bird flu. Her 10-year-old brother had died 3 days earlier with respiratory symptoms, but no samples had been taken, so that his death does not appear in the WHO statistics (WHO, 2006b).

Three cases in Thailand in 2004 were uncovered only later, by accident, during investigation of another pneumonia death at the same hospital (Ungchusak et al., 2005). In this incident an 11-year-old girl, who died, infected her mother, who died, and probably her aunt (though the aunt also had exposure both to sick chickens and the sick mother), who recovered. The mother's and aunt's cases were confirmed as bird flu, but the limited samples from the dead girl were not sufficient to show what killed her. So these three cases, with two deaths, were nearly missed altogether, and the girl's case is still not counted in the WHO statistics of "laboratory-confirmed cases."

In February 2003, a member of a Hong Kong family fell ill and died while the family was traveling in China's Fujian Province. Later, two other members of the family tested positive for bird flu. Flu is suspected in the one who died while traveling, but again, this case is not counted in the WHO statistics (Normile, 2006).

In January 2007, a 22-year-old woman from Lagos, Nigeria died of bird flu. Her mother had died with similar symptoms 12 days earlier, but, again, no samples had been taken, and so yet again her death went uncounted (WHO, 2007b; WHO, 2007c).

In yet another Indonesian village, a 20-year-old man fell ill with bird flu. One day earlier his brother had developed a respiratory illness; however, the brother died before any samples could be taken. Consequently, his death was not counted. A 15-year-old sister developed flu symptoms at about the same time, but tests indicate she had ordinary flu (WHO, 2006f). This family presented a dangerous opportunity for bird flu to recombine with human flu, perhaps producing a variant that could spread easily. Fortunately, it did not occur. It also points up the difficulty of guessing about causes of death when there are no samples available. However, deaths from ordinary flu in people of the ages we have been considering are extremely rare, and I think it can be stated with a good degree of certainty that either all these uncounted deaths were due to bird flu, or that at most one of them might have occurred from some other cause.

I came across most of these missed or almost-missed cases by accident, while researching other aspects of this paper. Someone who specifically looked for such cases would likely find several more. As of the end of May 2007 (when I wrote this section), there had been only 187 confirmed deaths. It is evident that an appreciable number of deaths are being missed in these statistics. And how many others there might be that neither I nor anybody else can find, because bird flu was never suspected and the lucky breaks that uncovered most of the sets of cases above did not occur, is completely unknowable.

So despite my suspicion that the WHO list exaggerates the mortality by overlooking the mildest cases, the deaths that are missed work to understate the mortality. And both the very mild cases and the deaths may be being missed disproportionately often, inasmuch as it is much easier, if suspicions arise later, to go back and check a survivor than it is to check someone who has died and been buried or cremated. All eight sets of examples listed above involve cases in which bird flu could not be confirmed because the patients had died. It is likely that if everyone had survived, all these missed cases would have been confirmed as bird flu and been added to the statistics.

We know there are many deaths. If there are sufficiently few mild cases, the bias in the statistics may be the opposite of what I am assuming. When counted cases include 60 percent deaths, it is likely the counted mild cases are less than 1/6 as numerous as deaths (since surely most of the 40 percent who did not die at least had serious cases). It would therefore take a considerably larger fraction of missed mild cases than missed deaths to keep these missed cases from causing the true death rate to be even higher than what we have counted. If serious cases are all counted but half of all mild cases and half of all deaths are missed, then if we count 60 deaths, 30 serious cases, and 10 mild cases, for a 60 percent counted death rate, the true death rate would be 120/(120 + 30 + 20) or 70.6 percent. If 10 percent of all actual deaths are missed (in an example where we have counted 60 percent deaths, 30 percent serious cases, and 10 percent mild cases), then the true death rate will be over 60 percent unless more than 30.8 percent of the actual mild cases are also being missed.

In epidemics of most diseases, even the most serious ones, there are cases of subclinical infection, where even though antibodies and other tests can prove that an infection has occurred, no symptoms are produced. Even in serious diseases, this can be a large fraction of the infections. However, according to one of the world's top flu experts, Robert Webster, for the case of bird flu, "there has been little or no evidence of subclinical infection in

humans" (Webster and Govorkova, 2006). WHO reports two subclinical cases detected through contact tracing of overt cases out of the first 256 confirmed cases (WHO, 2007a; WHO, 2006g). However, of the 41 cases in 15 family clusters (plus two nurses, making 43 cases in all) included in Olsen et al. (2005), testing uncovered 3 asymptomatic cases. These 43 cases included 25 deaths and 9 cases where the outcome was unknown.

There is still another consideration: a death calls in the authorities and triggers investigations in a way that simply being sick, even life-threateningly sick, but with ultimate recovery, does not. At least in certain social circumstances, this may make deaths disproportionately likely to be caught, rather than missed.

Finally, some governments may wish to cover up their cases of bird flu, fearing repercussions on the tourist industry or other economic setbacks (Normile, 2006). They would presumably find it easier to cover up mild cases than serious or fatal ones. They don't have to actively cover up in order to bias the statistics toward the most severe cases. All they need do is not go out of their way to look for cases.

Perhaps the best evidence occurs when there are multiple cases in the same community. Once the community becomes conscious of the outbreak, sick members will be much more likely to seek help, and national and international teams will be sent to scour the area for more cases. These teams will do antibody testing and use other methods that will likely find even many of the mild cases who do not seek medical help. All or nearly all of the cases, mild or severe or fatal, will then be counted, and mortality rates for these cases should be reasonably accurate.

As numbers of cases increase, we will be able to get a better indication of what the actual mortality rate is. Awareness of the disease will penetrate into ever more remote locations, so that more recent statistics may be more accurate than earlier ones. More significantly, as cases occur in more developed countries many fewer of them will be missed, and therefore the mortality in developed countries may give a better indication of what the overall mortality is, at least in the presence of top-notch medical care. Confounding this approach, however, will be the fact that different strains will get started in different geographic areas (as bird populations with varying strains start infections various places), and mortality may vary significantly from strain to strain.

11.3.3. Pandemic bird flu death estimate

If, therefore, we use an estimate of 30 percent of the world population, or 2 billion, as the number of people who will come down with avian flu in the event of a pandemic, and if we assume the mortality rate will not change appreciably from what it has been with the cases that have occurred to date, but that the current statistics somewhat overstate mortality by missing mild cases, and if we therefore reduce the current mortality from the latest WHO chart of 58.5 percent (WHO, 2011) down to 50 percent, then we arrive at 1 billion for a medium estimate of worldwide deaths to be expected from an avian flu pandemic. It might be less if the pandemic virus is a bird-human hybrid.

In reducing the death rate down to 50 percent, I am really being rather generous, since many if not most of the cases that make up the WHO statistics have been hospitalized and received intensive medical care. In the event of a worldwide pandemic, very few victims will receive this level of care, because cases will be many times what the facilities can

handle, even when they occur in the richest and most developed countries of the world [37].

I am also ignoring the potential danger that as the virus spreads person to person, becoming better and better adapted to growth within human tissues, its virulence will increase as its concentration within the tissues it infects increases. This does not have to happen, but it certainly can.

And while I do not know how to give any estimate, surely it is obvious that a billion deaths occurring within just a few months (and the sickness of many others and the ensuing panic) will cause catastrophic social failures sufficient to kill many more.

11.4. The role of AIDS

Finally, if the epidemic does materialize, and if it does so as a result of AIDS, and if a billion die because of it, how many of these deaths should we attribute to AIDS? After all, in the absence of AIDS perhaps the epidemic would just have started a month later.

My view is that the great majority of the deaths should be attributed to AIDS. So far, after more than 7 years of H5N1 bird flu in poultry (not counting the 1997 outbreak in Hong Kong, which was of a different strain of H5N1), there have been only 556 verified human cases, with 325 deaths (WHO, 2011). This is a very small number. There is little evolutionary reason for cases in chickens to continue becoming more contagious to humans as time passes. Once adaptation to the stepping-stone of chickens (see Section 8.6.3) has changed a fecal-oral waterfowl virus into a respiratory virus with a predilection for the human-like receptors in chicken's respiratory tracts, further selection for spread in humans will occur only while the strain is residing in humans. (Evolution, recombination, and genetic drift in chickens will produce a number of varieties, and some will happen to be better able to infect humans than others; but there will be no progressive tendency towards better human adaptation, after adaptation to the chickens is complete.) Though the virus doubtless still has some improvements it can make in its adaptation to chickens' lungs, in view of the large number of chicken-to-chicken passages that have occurred it seems likely that the major part of this adaptation is already past. Therefore, I would expect the number of human cases caught from birds to continue to accumulate at quite a slow rate, which over the last seven calendar years (2004-2010) has averaged 6.1 per month (WHO, 2011).

In the absence of AIDS, I doubt that this is fast enough to cause a transfer to happen during the time when this current, deadly strain is still around. If it does happen, it might well be several years later than a transfer occurring as a result of AIDS. But a several years' delay would allow precious time for us to prepare, possibly to develop and produce and distribute an effective vaccine that could nip any incipient epidemic in the bud. The resulting deaths might be a tiny fraction of those that would occur in the event of an AIDS-assisted transfer several years sooner.

And even an AIDS-assisted transfer might not be imminent. If it does not occur for a few years, the death toll may be a small fraction of the 1 billion I gave as a plausible estimate above. One reason I have written this paper is to show that typical death estimates are often woefully too small, by an order of magnitude or more. And one reason for wanting to expose the deficiencies in typical estimates, despite the serious discomfort, not to say fear, this may generate, is that I do in fact just precisely hope to engender serious discomfort and considerable fear. These may be dreary, but if they can finally wake us from

our pleasant dreams, perhaps enough effort might be made to actually achieve the medical breakthroughs that could change the 1 billion deaths into, say, 10 million, thereby saving 99 out of every hundred who would die if the pandemic occurred today.

Unfortunately, as we saw in Section 8.6.3, Greger (2006) has given very powerful arguments showing that in fact it is modern factory farming that has produced the incredibly deadly current strain of bird flu, that it did so through simple and repeatable means which in fact have been happening with other bird flu strains more and more often in the recent past as factory farming has replaced traditional farming, and that it will inevitably continue in the future to produce other deadly strains, so long as factory farming continues. Consequently, it seems near certain that our species will sooner or later fall victim to one of these factory-farm-bred killer strains, with or without the help of AIDS.

There is only one comforting thought that I think at this point is still sustainable: the current, horrendous bird flu is so far outside the norm, we are entitled at least to maintain some hope that perhaps another one this bad will not come about for centuries or millennia. I think this speculation is decidedly unlikely, but there have not yet been enough examples for us to say how often a strain on a par with this worst-ever one might arise. There is a small chance it might be almost never.

In any case, unless rapid medical progress means that future pandemics are avoidable or of small consequence, the case made by Greger greatly increases the expected number of deaths due to AIDS. It greatly increases the number of highly pathogenic bird flu viruses to expect in chickens over the ensuing decades, and AIDS will likely transfer a far higher fraction of them into our species as pandemic human viruses than would have occurred in the absence of AIDS.

Of course, if we lose a billion people to the first pandemic, we may well outlaw factory farming and save ourselves from these future pandemics. But like the cigarette makers and lung cancer, the factory farm interests will likely fight tooth and nail to deny and suppress the fact that they brought this Armageddon to the world. I began working on this piece in early 2006, yet it was not until October 2009 that I belatedly discovered Greger's seminal ideas, ideas on which literally billions of lives may well hinge. Perhaps I am blaming suppression for my own shortcomings as a researcher, but at least to me it seems the factory farmers have so far been pretty successful.

As a result of discovering Greger's work, I have significantly modified this current subsection, compared with the first published version. However, the next section needed so little change, I am only adding note 38 and updating the first paragraph. Even without the benefit of Greger, I had come to the conclusion that poultry farming needed to be stopped.

11.5. An idea worth exploring

If the transfer of bird flu to humans occurs, regardless of whether or not AIDS had a hand, primary responsibility will almost certainly fall upon the poultry farmers. Very few of the human cases to date caught it from a wild bird, the only example I am aware of being 7 people in Azerbaijan who became infected after defeathering wild swans that had died of bird flu (WHO, 2007d).

Is it not strange, then, to hear the same epidemiologists who predict disaster express worry about what might happen to the poultry farmers if in panic people stop buying

chickens? If we are very lucky, so many poultry farmers might go out of business that the epidemic never occurs. I am sure providing jobs for the world's poultry farmers is worth a few deaths. Perhaps it might even be worth a million deaths, though anyone arguing so would have a considerable uphill struggle to make a case. But no sane person could argue it was worth 100 million deaths; yet deaths might easily be more than 10 times that number.

I have not looked into this, but it would seem to be an idea worth exploring: How much would it cost to buy out all the world's poultry farmers? Even if all other countries opted out, it would surely cost the United States all by itself far less to buy out all the world's poultry farmers than it would cost to undergo a major epidemic with 15 percent of its people dying directly from the flu and with social breakdown taking many more lives and costing much more money that could have been spent buying out the farmers. Poultry farmers could be paid a fair price, or even an exorbitant price, to retire or change their line of business. Then it could be made illegal to raise, buy, sell, or eat poultry. If there were some other extremely dangerous practice that stood to kill more people than most estimates of a nuclear war, would we not make such a practice illegal? The practice already killed 50 million of us in 1918 [38], more than twice the 21.5 million total deaths, military and civilian, to both sides in World War I, and, as I said earlier, either the largest or the second largest loss of life from any cause in human history, the competition with World War II being too close to call. But when the deaths from World War II extended over nearly 6 years, and most of the deaths from flu occurred in less than 6 months, I would have to give the 1918 epidemic the edge.

According to Michael Osterholm, writing in the *New England Journal of Medicine* (Osterholm, 2005a):

> It is sobering to realize that in 1968, when the most recent influenza pandemic occurred, the virus emerged in a China that had a human population of 790 million, a pig population of 5.2 million, and a poultry population of 12.3 million; today, these populations number 1.3 billion, 508 million, and 13 billion, respectively. Similar changes have occurred in the human and animal populations of other Asian countries, creating an incredible mixing vessel for viruses. Given this reality, as well as the exponential growth in foreign travel during the past 50 years, we must accept that a pandemic is coming – although whether it will be caused by H5N1 or by another novel strain remains to be seen.

But perhaps the reality he speaks of can and should be changed [39].

12. Appendix: A consideration of two potential objections

There are two objections that I think will occur to many readers, a discussion of which takes us too far afield to conveniently include within the text.

12.1. Objection 1

"AIDS patients, with their already very tenuous grip on life, will die so fast of any *bad* new infections that they will be unlikely to pass them on. There may be a theoretical risk of the sort of transfer you suggest, but this simple fact will keep the number of such transfers to a minimum."

1) It is conceivable that this is valid for the rapidly-fatal diseases such as Ebola, Lassa, Marburg, and Nipah. This may be why they have not yet entered through the AIDS victims they have quite possibly already infected. (However, I strongly suspect it is because they have not yet encountered quite the right set of conditions, or undergone quite the right set of mutations. They are rare infections and have not yet had more than a handful of opportunities, and perhaps none at all.) It is not valid for slow viruses such as SIVs and the non-lentivirus immunodeficiency viruses of monkeys, or such as scrapie and undoubtedly other very, very frightening pathogens. In my view, slow viruses that are successfully transferred present a significantly greater long-term danger than the rapidly-fatal epidemic ones, for several reasons, including the fact that flu, Ebola, etc., will likely cause one-time epidemics and then cease to exist in our species; the fact that slow virus diseases may not be detected until well past the time they could be stopped, perhaps spreading worldwide, as HIV did, before we even become aware that the transfer has occurred; the fact that slow-virus diseases exploit fundamental psychological weaknesses of our species which prevent us from acting decisively to combat slow-motion disasters, however great they may ultimately become (as with overpopulation, global warming, deforestation, species extinction, and, of course, AIDS itself); the fact that slow-virus immunodeficiency diseases will likely bring other new diseases along with them; and the fact that slow-virus immunodeficiency diseases will provide HIV with a hypersusceptible substrate in which to perfect new methods of spread and to develop new evolutionary potentialities it could not otherwise have accomplished (and vice versa).

2) It may not be valid for rapidly-fatal bird flu, if the arguments of Robert Webster (Section 4.2.1) are correct, that bird flu might survive longer in AIDS victims than in normal subjects, due to the fact that it is overstimulation of the immune system that usually kills in cases of bird flu.

3) Even a pathogen which causes a serious illness in its normal species of residence may be much less pathogenic to start with when it barely manages to infect its first AIDS patient and can scarcely survive. It will likely become more pathogenic as its adaptation to its new environment improves and it becomes able to infect a greater range of cells, to greater concentrations, with greater ease and rapidity.

Here is a suggestive quotation from Barry (2004, pp. 176-177):

> In 1872 the French scientist C.J. Davaine was examining a specimen of blood swarming with anthrax. To determine the lethal dose he measured out various amounts of this blood and injected it into rabbits. He found it required ten drops to kill a rabbit within forty hours. He drew blood from this rabbit and infected a second rabbit, which also died. He repeated the process, infecting a third rabbit with blood from the second, and so on, passing the infection through five rabbits.
>
> Each time he determined the minimum amount of blood necessary to kill. He discovered that the bacteria increased in virulence each time, and after going through five rabbits a lethal dose fell from 10 drops of blood to 1/100 of a drop. At the fifteenth passage, the lethal dose fell to 1/40,000 of a drop of blood. After twenty-five passages, the bacteria in the blood had become so virulent that less than 1/1,000,000 of a drop killed.
>
> The virulence disappeared when the culture was stored. It was also specific to a species. Rats and birds survived large doses of the same blood that killed rabbits in infinitesimal amounts.

This is all about adaptation to new environments – rabbits, rats, and birds – and it is by no means the only dramatic example. However, by artificially infecting successive animals, it exaggerates what is likely to occur in nature, since the pathogen can concentrate solely on growth within the body without having to concern itself with adaptations that favor its spread to other bodies. These two sets of adaptations will likely be in some degree of conflict, so that we would not often expect such extraordinary changes in virulence as this (Levin and Svanborg Edén, 1990).

However, the 1976 outbreak of Ebola in Zaire killed 88 percent of those it infected (Fisher-Hoch, 2004). A later outbreak among laboratory monkeys in Washington, DC infected several monkey handlers, according to antibody tests, but they never even became sick (Preston, 1994, pp. 251-254). The conclusion some scientists drew was that this was a different strain of Ebola which was unable to sicken human beings. While this is certainly possible, it is also certainly possible that if these infected monkey handlers had passed their infection on to other humans, and they to still more, that after a few generations of transmission, and of adaptation to growth in its new medium, its virulence would have increased from no symptoms at all to killing 88 percent or more of them. We do not know, after all, whether there were earlier, asymptomatic or less symptomatic, cases in Zaire before the ones where 88 percent died. I think this is rather likely. And if so, it would also constitute a very dramatic increase in virulence.

Interestingly, Barry goes on to comment on this very question: He says that Ebola, as it passes from person to person, "becomes far milder and not particularly threatening" (Barry, 2004, p. 177). While I do not doubt that it is sometimes possible for pathogens to evolve in the direction of less pathogenicity, I think he is probably mistaken in the case of Ebola. He does not cite a reference. I found one, but it contains too few cases, the trend is ambiguous besides, and there are alternative explanations for the trend even if it exists. Perhaps he has a better reference, but I will be rather surprised if it is valid [40].

Many pathogens may in fact cause little damage in their unadapted state when they first are transferred. They may not even cause much damage when they first become human infections, able to survive without the help of AIDS. (Like many opportunistic infections of AIDS patients, they may by that time cause serious problems when in AIDS patients but

have little or no adverse effect on those with normal immune systems.) But as the years pass and their ability to grow within the human body improves, their pathogenicity will likely increase apace.

There may be a limit to how much an organism's pathogenicity can increase as adaptation to its new host progresses, inasmuch as killing the host too quickly might prevent spread to secondaries. But this limit will not become operative until the disease is severe enough to start killing a substantial proportion of its victims. And this is pretty severe.

12.2. Objection 2

This brings us to the second objection to be addressed in this appendix:

"Your estimates of human deaths from a bird flu epidemic are likely much too high. Currently, the mortality may be as high as half or two-thirds; but precisely because it is so high, this strain cannot become epidemic – it will kill itself off as it kills its victims. It will have to lose much of its deadliness before it will be able to spread efficiently enough to be a problem. Perhaps when it does, it will be no deadlier than the typical flu we get every year anyway."

I have seen similar ideas expressed many times over the years, but I have never seen them defended against what appear to me to be very serious objections.

1) To begin with, I point out that the extremely high mortality rate due to bird flu among infected poultry is not preventing the disease from causing extremely difficult-to-control epidemics on poultry farms. In fact, among poultry, mortality can approach 100 percent (Garrett, 2005).

2) Rinderpest is a virus of cattle and other ruminants. It is related to measles in humans and distemper in dogs. It is both extremely contagious and extremely deadly. "In a fully susceptible population, as is the case in non-endemic areas, morbidity and mortality can approach 100 percent" (Obi et al., 1999, p. 5). An epidemic "in the 1890s wiped out 80-90 percent of all cattle in sub-Saharan Africa" (UN Food and Agriculture Organization, 1995, p. 64).

3) Smallpox is one of the oldest recorded diseases, being known from the time of the Pharaohs. It managed to infect a substantial fraction of the human race for several thousand years; yet when finally vanquished in 1977, it was still killing about 25 percent of those it infected. Smallpox has no animal reservoir. The last cases in 1977 were direct descendants of the first human cases thousands of years before. The disease had thousands of years to become mild – more than 50,000 successive human-to-human passages – yet that was as mild as it got.

4) This last raises the point that there is a large difference between a disease such as smallpox, which has thousands of generations to adapt, and a one-time epidemic, such as flu, which will have perhaps 200. (It would only be around 100 but for the fact that the flu seasons in the Northern and Southern Hemispheres are six months out of phase, so that as the last generations are dying out in the one hemisphere, they give rise to another whole series of generations in the other. But note that the 1918 flu swept the entire world simultaneously, with most of its deaths occurring in only twelve weeks near the end of 1918 (Barry, 2004, p. 397).) Even if it is true that bird flu might eventually, if it lasted long

enough, greatly reduce its lethality, how much will it be able to accomplish during a pandemic lasting perhaps one year? (Proponents may say that this is beside the point; that too lethal an epidemic will not kill anybody, because its rate of transmission will be below 1, which means the epidemic will never exist. I will address that below.)

5) For smallpox and most other serious epidemic diseases, infection produces long-lasting immunity. This is also true for each particular strain of flu (though there is limited cross-protection against infection by other strains). When an individual becomes immune, it is almost the same for the pathogen as if the individual had died. These serious epidemic diseases have managed to do very well for a very long time "killing" virtually all those they infect, usually within a few days.

6) It is true that to a certain extent there is a conflict between selection for most rapid growth within the individual body (which is presumably bad for that individual) and selection for most rapid spread to other bodies. Despite this, there is nothing to say that a pathogen that goes all out for rapid growth within the individual, thereby reaching extremely high titers, won't spread to more new individuals as a result of these high titers even though it kills every single individual it infects, than a variant that doesn't kill anybody because it is much more innocuous. There is nothing to say it won't spread to more new individuals than any other variant, period. There is greater spread per time period, but for a shorter time. Will this result in more new victims per case, or fewer? The answer is not clear, and will presumably vary from pathogen to pathogen.

The pathogen within each individual body is living under a death sentence anyway. Its existence will come to an end in a short time regardless of whether the immune system defeats it or whether it defeats the immune system (and kills the patient). It may be that the most efficient evolutionary strategy is to reproduce to the maximum extent possible, generating the highest titers possible, causing worse and worse effects on the patients as this strategy evolves through successive victims, until the point is reached that in fact the patient would die, but with an average time of death just slightly longer than the amount of time the pathogen would survive until destroyed by the patient's immune system. If the immune system normally destroys the infection in 8 days, then perhaps a strain that halts its drive toward higher titers and greater virulence at the point that the patient would die in 9 days will spread to more new victims than a strain that kills in 7. This, when it works exactly right, will allow most rapid spread to other hosts without reducing the time during which this rapid spread is occurring. But there will be many cases where the immune system is a bit slow and needs 10 days. Or the patient is weak and dies in 7. In these cases, the pathogen would have done (a little) better if it had been a little less virulent. Rather than selection in favor of mildness, this would indicate selection in favor of virulence, but stopping just short of being fatal for the majority, while killing an unlucky and not negligible minority. In the cases of infections that started out being too virulent, selection would moderate the severity until this optimum point was reached.

7) There are other selective forces that will favor greater lethality. One prime time for a dangerous infection to spread is before symptoms develop, when patients will be up and about and mingling with the public and neither they nor their potential victims will realize the danger. Perhaps one means of accomplishing this would be for the pathogen to reproduce extremely rapidly, hoping to attain high titers and to spread before the immune system can respond with the fevers and inflammation that often both combat an illness and signal its presence. If this extremely rapid reproduction could lead to even 1 further infection before symptoms develop, then this variation will be successful even if every

patient subsequently dies from the massive onslaught. I can think of potential problems with this scenario and am therefore unsure how realistic it might be. But another prime time for spreading does seem to provide a realistic scenario for the selective favoring of deadly strains over milder ones. I think it may be important.

This other prime time for an infection to spread is *after* symptoms arrive, *after* the patient is very sick, *after* he needs medical care. The next prospective victim is the medical caregiver. The intimacy of the contact required in caring for a very sick patient makes the caregivers ideal targets. Not just doctors and nurses, but family members are at risk here. In a widespread pandemic, almost all care will be given by family members, because there will be many times more patients than the doctors can possibly treat. And the family members will not be in a position to employ many of the procedures available in hospitals to limit exposure of caregivers.

In this scenario, the best strategy for the human race is to try to find people who have already recovered from the illness. They will be immune. They can give as much care as they like, with virtually no risk to themselves. This will block one very important part of the pathogen's strategy for finding new hosts.

But the pathogen can fight back. If it kills every single victim, there will be no immune caregivers to foil its future spread. In many cases, it can do this with very little cost to itself, since its sojourn in each individual victim, which it can either kill or spare, will come to an end shortly, regardless.

This is too extreme a strategy. In such a case, there will be very few caregivers. When the patient cannot be saved anyway, when palliative care can only be given at great risk to one's own life, and to the lives of loved ones whom the caregiver might inadvertently infect (and those they might infect...), then in most cases there will be no care given. Patients will be abandoned, or possibly shot or otherwise safely euthanized. Indeed, when the choice is between a quick, painless death now and an agonizing one over the next few days, it is likely patients will beg to be shot. There will be much less care given and much less opportunity for the infection to spread to caregivers.

But what about a strategy of killing 90 percent of victims? Many spouses, children, parents of a victim would be willing to risk their lives for even a 10 percent chance of saving their loved one. But many would not.

I do not know what the pathogen's optimum strategy would be, but I suspect it would be optimum to kill more than the approximately 50-60 percent that bird flu has killed so far. If it kills 75-80 percent, it has halved the number of immunes it creates; yet I suspect most loved ones would be willing to risk their lives for a 20 or 25 percent chance of regaining their beloved.

In order for this strategy to work, the pathogen needs specifically to be helping its *offspring* [41] pathogen to infect cases, not merely helping other examples of the pathogen in general, which are in fact its competitors in a race to devour their common food supply. (If it helps a non-descendant to infect someone, that is one less target that its descendants can infect. Indeed, if the helped competitor produces descendants of its own, it may turn out to be a lot more than one. The strategy has not only helped its rival, it has hurt its descendants.) But this condition appears to be met. Infection will often come from family members, and caregivers will often be family members. All the sick family members may well have the same strain. If 75 percent of them die, as opposed to 50 percent, there will be only half as many immune caregivers to assist with the strain's subsequent victims within the family, and the likelihood of recruiting still-susceptible family members as caregivers

will increase. If families are thought to be too small, the same analysis will work for communities. Even if two or more strains are raging within the community, the viscosity, or lack of random mixing, will see to it that the strain practicing this particular strategy is disproportionately helping its own descendants.

We have just considered two of the most important periods in the life of the infection: before the first telltale symptoms begin, and during caregiving. In the first (admittedly somewhat weak) case, fatalities are not intended but are merely a byproduct of selection for the fastest possible reproduction. But in the current case (far stronger, I believe), it is fatalities that are specifically being selected for. The pathogen wants to make the patient very sick, so that he will need lots of medical care, presenting many potential chances for further spread. Then it wants to kill the patient, in order to eliminate a distinct danger to its offspring, which will exist if the patient lives and can provide medical care to victims sickened by those offspring, or their offspring, depriving them of a potential source of future spread, which they would have if the caregiver were not immune.

It is ironic that the greater the devotion of family members and the greater the degree of social cohesion, the more it benefits the pathogen to be highly lethal. Some societies, such as perhaps the Chinese, are much more family-oriented than others, such as perhaps the Americans, with their frequently fragmented and dysfunctional families. Assuming my opinion of the relative cohesiveness of Chinese versus American families is correct, selection will favor strains in China that are more often fatal than those that are favored in America. Chinese will likely continue to care for their sick, despite risks to themselves that would prompt most Americans to abandon their sick.

And since non-human animals seldom care for their sick at all, there is no advantage to making the animal either very sick or killing him.

8) The fleeing to uninfected areas that occurs when a terrible epidemic strikes very greatly speeds up its spread, and this may select for the most terrifying strains. However, the worst strains will also most diminish temporary travelers coming in, and this is another principal mode of spread. In times and places with little travel, the second effect might be insignificant; but in cases such as Bethlehem or Mecca, travel would likely outweigh fleeing. The worst strains will also call forth greater societal efforts to stop the disease. In epidemics where society's maximal effort is being called forth anyway, still-worse strains would not incur this cost. There is also the fact that organized societal responses may sometimes be counterproductive, as I believe has especially been true in the case of AIDS. There are still other complications, but I think it is safe to say that different societies in different times and places will respond very differently when faced with a killer epidemic, so that in certain cases the most deadly strain may come out on top, while in others it may fail.

9) There is another strategy that might tend to increase fatalities, both among humans and animals (and, for that matter, plants). As stressed early in this paper, there is a great excess of life born beyond what the environment can possibly support. With each average generation (I say average because of the possible exception of short stretches when conditions are unusually favorable), the majority, often the vast majority, must die. There are a limited number of spots in the population available to each generation, and when the number born greatly exceeds this number, as it normally does, then these spots are fought over in a literal life-and-death struggle. If one member of the population survives a severe infection, then (on average) one other member, who could have occupied the vacated spot had the sick member died, will be without a spot and will have to die instead. If the one

who dies for want of a spot was susceptible to the infection, and the one who survived it is now immune, then this population is less favorable from the point of view of the infecting organism than if the sick one had died and the susceptible one had survived. If instead of producing a non-susceptible, the infection kills this victim, there will be an extra spot in the population that can be taken by a susceptible. If a farmer owns an orchard full (*completely* full) of fruit trees, and these trees produce fruit for thirty years and then become too old to yield any more, the farmer would do well to remove those trees that have already produced all they are going to, so that new trees can spring up in the spots they were occupying. A non-susceptible host organism is to the pathogen what an old fruit tree is to the farmer.

Because animals and plants generally reproduce much more excessively than human beings, this strategy might be more applicable to them. They can be killed at a far higher rate before their numbers will begin to decline. At least in certain cases I think such a strategy could outcompete a less-lethal strategy, and indeed that 100 percent lethality might be optimum in some of these cases. It might be necessary for some extraneous factor to hold the pathogen to a low level. However, I think density-dependent factors could also probably work, especially in the case of pathogens with relatively long generation times and hosts with relatively short ones, and that in such cases the fraction infected needn't necessarily be low, and indeed that even 100 percent infection with 100 percent lethality is compatible with survival of the population so long as at least a few of the fatalities occur after the beginning of the reproductive period (recall that the salmon population manages to survive despite less than one salmon in a million living long enough to reach the reproductive period), and that in the context of what we are discussing here there is no requirement that the population must survive, anyway – there is nothing that says that selection cannot bring about the evolution of a strain that will utterly consume its food supply and cause its own extinction.

If there is a problem with this strategy, I think it likely involves insuring that the strains that benefit from the strategy are the same ones as cause the extra fatalities. In relatively non-mobile populations, the extra susceptibles will probably be close by (imagine the fruit orchard), and thus will be disproportionately likely to come down with the strain that produced the empty spot.

Here is another way to think of it: diseases that produce immune survivors tend to exhaust their population base, as it becomes more and more immune, forcing them to find new populations to infect. Look back at the two examples with differing population density I gave in the section on Influenza Death Estimates (Section 11.2.2). In the first example a new disease with an inherent transmissibility of 2.0, starting off as a single case, infected 869 out of 1000 susceptibles, leaving 0.869 of the population immune, 0.131 still susceptible (and no deaths). If population density was increased to the point that the transmissibility rose to 3, then all 1000 became infected. But in neither example could another single case start another epidemic until the proportion of susceptibles substantially rose. Even if the 1000 individuals of example 1 were crowded together after their epidemic until the inherent transmissibility rose to 3.0, when there are only 131 susceptibles each case would infect only 3 x .131 further cases, not even half enough to maintain itself, let alone start an epidemic. It would require an inherent transmissibility of 7.6 new cases from each old one before another introduction could even maintain itself in a population which is only .131 susceptible.

The immune fraction is diluting the population, making it harder and harder for the disease to keep going. But if the disease kills 100 percent of those it infects, and if the

population can be replenished with susceptibles either from the excessive reproduction of the population itself, or from other, neighboring overcrowded populations being forced into the vacuum, then there is no dilution and the infection can keep going. There is no longer the necessity for the infection to find new populations to invade; the new populations will find the infection.

I have not pursued this example in detail, but at least in certain circumstances (e.g., mosquito-borne diseases along riverbanks in otherwise dry areas) I think it could work, and that it might work even in far less restricted circumstances.

10) A plausible modification to the strategies of rapid growth given in 6) and 7), above, could select for lessened mortality. Suppose the pathogen specializes for growth only in those particular tissues that are likely to lead to spread to other hosts. Such specialist pathogens ought to be able to outcompete their more general rivals within these tissues. And if the generalists outcompete them in all other tissues, it doesn't matter. And if the specialists, thereby, are the ones that are best at infecting new hosts, these new hosts may well become less sick than the earlier hosts, who had many more of their tissues under assault. Flu most often spreads via the lungs, and of course the lungs are a vital organ. But it has got to be better for an organism to have one vital organ under attack rather than all of them.

Perhaps this strategy might explain why colds are so seldom fatal: they are most apt to spread via nasal secretions, and therefore specialize in growth within the nasal passages, and these are not a vital organ. Colds do not attack the heart or liver or other organs that do not aid in their spread. When a new pathogen kills through attacks on organs that do not aid in its spread, selection *may* produce a milder strain as time passes. But since we saw in 7), 8), and 9), above, that fatalities may be actively sought, it is also possible that attacks on vital organs that have nothing to do with spreading the infection might be favored.

11) There is another strategy that is capable of modifying the most rapid growth strategies. Suppose instead of devoting all its resources to rapid growth, the pathogen concentrates instead on producing offspring that can survive for the longest time outside the body. This might be a win-win situation: more successful for the pathogen and less damaging to the host.

However, this strategy is unlikely to result in much amelioration. The new pathogen has much adapting it can do to the new environment it finds itself in while in the body of its new host. But the outside environment is probably very much like the outside environment it encountered for countless generations while in its old host. Adaptation to that environment will likely already be almost complete. The adapting that occurs will mainly be concerned with better growth within the host, and this is likely to be worse for the host, unless specialization for target organs outweighs it.

12) Much of the apparent "adaptation" of potential killer viruses that makes them milder is in fact adaptation of the infected population to the virus, rather than the other way around. Year after year the most susceptible 25 or 50 percent of infectees are killed, until the only ones left are those able to fight off the attack. This is a very hard way to ameliorate a disease, and it will not apply at all to a virgin-soil epidemic, such as bird flu will be and such as new human diseases transferred from other animals. When a new pathogen attacks a virgin population, the death rate can range all the way up to 100 percent, and the pathogen may still be so highly contagious as to infect up to 100 percent of potential hosts. Very close to this is what happened when, in 1950, the very mild myxoma virus of South American rabbits was deliberately introduced into Australian rabbits that had never seen it

before. Billions of rabbits died of myxomatosis; and in those areas best suited for spread of the virus, the rabbits were very nearly wiped out: one population that had been estimated at 5000 was reduced to 50 within a month. After being so nearly exterminated, for quite a number of generations, the rabbits are now showing enough resistance that probably more than half of them are able to survive myxomatosis. But this did the first generation that originally encountered the virus no good at all.

The virus itself, after first falling in virulence (to 70-95 percent lethality), as it adapted more rapidly than the rabbits, is now back up to more than 99 percent lethal, not against resistant wild rabbits, but against rabbits who have not encountered the virus before and who have not experienced the loss of the great majority of several successive generations due to its effects (Fenner and Fantini, 1999, see esp. Chapter 14).

13) Even this apparent amelioration through killing off the most susceptible does not have to happen. At one time the American chestnut grew throughout most of the eastern United States and was the dominant tree of the Appalachian forests, making up an estimated one tree in five. In good regions they grew 120 feet (37 m) high. The largest trees had trunks over 10 feet (3 m) in diameter, and occasional giants considerably exceeded this size. Gifford Pinchot reported seeing 13-foot trees, and a single example is recorded of a 17-foot-diameter (5.2 m) tree in North Carolina (Detwiler, 1915). In flower, it was very beautiful. It was fast-growing, and its lumber was strong and easy to work. The trunks were often almost perfectly straight. Without any treatment, the wood could survive contact with the ground for decades without rotting, making them ideal for telephone poles, railroad ties, split-rail fences, piers, and house construction. The bark provided the bulk of the tannin used in the U.S. leather-processing industry. And of course the nuts were abundant, nutritious, and an important source of food and income for the local populations.

Sometime around 1900 the chestnut blight (a fungus) was inadvertently brought over in Japanese chestnut trees, which were highly resistant. But the virgin-soil epidemic that erupted when the blight spread to the American chestnut surpasses even myxomatosis in the Australian rabbits.

It was first detected in New York City's Bronx Zoo in 1904. By 1912, all chestnut trees in New York City were dead. It spread like wildfire to include the whole range of the chestnut. "Dead" stumps may continue to put out new shoots for many decades, but within a few years, almost always before they can flower and reproduce, these too have been infected and killed. According to an unreferenced article on the American chestnut in Wikipedia (accessed 6 August 2008 at http://en.wikipedia.org/wiki/American_Chestnut), today there are probably fewer than 100 trees with trunks as large as 60 cm (24 in) left within its former range.

A new actor has now entered the picture: a virus that attacks the fungus and weakens it to the point that trees can often survive. The virus must be artificially spread, but perhaps with our and its help, the species may survive. But before the virus's discovery in 1951, it looked very much as if the blight would utterly exterminate the American chestnut. In 1900 there were an estimated 3 to 4 billion American chestnut trees. If this blight was not 100 percent infectious and 100 percent lethal, it certainly came very close. (Davis, 2006; Smith, 2000; Lutts, 2004)

And it is not only plant species that can be driven to extinction by novel pathogens. Amphibians are decreasing alarmingly all around the world. Since 1980, 122 species are believed to have gone extinct, and the actual number may be significantly greater than that (Gascon et al., 2007, p. 59). Though climate change and pollution have contributed, a

chytrid fungus of African frogs is believed to be the largest factor behind the massive decline of amphibians, which are going extinct "at a rate unprecedented in any taxonomic group in human history" (Gascon et al., 2007, p. 4). This fungus was unknown until the investigations of the amphibian die-off revealed it. Like the chestnut fungus, this fungus was spread into new populations that had never encountered it before by human actions, starting with the worldwide use of those particular African frogs in 1935 in a newly-developed human pregnancy test (Weldon et al., 2004). This is the first species of chytrid fungus that has been shown to infect vertebrates (Daszak et al., 2007), yet with our help, and the help of never-exposed amphibian populations all over the world, it has become "the worst infectious disease ever recorded among vertebrates in terms of the number of species impacted, and its propensity to drive them to extinction" (Gascon et al., 2007, p. 59). Likewise, we had never heard of SARS, or HIV itself, until people started dying from them. It is seriously wrong to think we are at risk only from the few dozen *common* and *well-known* infections of AIDS patients.

This example, the chestnut example, the myxomatosis example, AIDS in humans, and the various new pathogens AIDS will bring with it, including possibly bird flu, are all transfers of pathogens from one species into another, leading to a virgin-soil epidemic. These can strike with a ferocity that is simply stunning, and the inviting of still more of them with procedures such as xenotransplantation truly astounds me. Have we learned nothing at all? Not even from AIDS?

The question of whether a new pathogen will become more deadly or less deadly as it adapts, and by how much, is not a simple one. It will vary from pathogen to pathogen, from host to host, and even within different societies of the same host if they exist under sufficiently different circumstances. I can see no grounds to take comfort from this fact. If a pathogen cannot spread within our species, the reason is unlikely to be that it is too deadly to do so.

13. A postscript and a complaint

The AIDS establishment and the journal publishers do not, as they would have you believe, originate, disseminate, and promote creative new ideas. Instead they go out of their way to stifle them, constructing a rigid orthodoxy that not only misses vital points but that contains much that is plainly wrong. They are able to get away with such behavior because you, their readers, let them. That is why it was so important to write this piece in a way that any reasonably intelligent person, willing to spend a little time and effort on the project, could understand. You do not need an expert to tell you whether it is right or wrong: you can see it for yourself. The experts all too often have hidden agendas or ulterior motives or strong biases, and in any case are the ones who have managed to survive and prosper within this system, which instantly renders them suspect. (When I earlier wrote of the psychological weaknesses that the slow viruses exploit, I very much had these facts in mind, among the others named there.)

HIV does two main destructive things: It fatally damages the immune system of those it infects and it lowers the immune system of the entire species, allowing it to become host to

an unknown number of new diseases. Without knowing how many or how bad the new diseases will be, it is not possible, *a priori*, to say which of these two destructive properties will be worse.

But HIV infects mainly risk groups, and these may amount to only a small fraction of the population as a whole: certainly this is true for the developed countries, and as the toll on the worst-hit countries, where the risk groups comprise anything but a small fraction, mounts, the insuperable costs will *force* radical changes in their societies, which, if adaptive, will greatly reduce the size of the risk groups there. On the other hand, the risk group for the new diseases AIDS ushers in may well be the entire population, and even if there is only one of of these new diseases, and even if it is only a quarter as lethal as AIDS, it may well kill more than AIDS kills directly.

My best guess, therefore, is that HIV's chief destructive property is not to kill those it infects but to kill indirectly through its progeny.

Indeed, if I am wrong, I think it will not be because the new diseases are far less significant than I have supposed here, but because HIV becomes casually transmissible, causing its risk group to encompass the entire human race.

And yet this idea about AIDS' weakening of the species immune system – possibly the most important single fact about the disease, and almost certainly one of the two most important – has gone unrecognized for over 25 years by an AIDS establishment that constantly congratulates itself on its tremendous progress.

But in fact it *hasn't* gone unrecognized. The earliest mention I have seen in print is in an article by William Haseltine of Harvard in the *New York Times*, 15 November 1992 (Haseltine, 1992). It contains a single sentence, "The ever-expanding population of immune-suppressed people with AIDS serves as a launching pad for new, highly infectious diseases," hardly enough to explain the fact to someone unfamiliar with it, but enough to show that Haseltine understood it at least by 1992. That was almost 19 years ago.

A more complete treatment (only three paragraphs, but they did explain it well enough to convince someone unfamiliar with it) was published in *Nature* in 2001 by Robin Weiss (Weiss, 2001a). Unlike the ambiguity with Haseltine, it is clear that Weiss recognizes the idea's importance. He saves those three paragraphs for a flourish at the end. And then over the next three years, he writes at least four other articles, all with the same flourish at the end, all either two or three paragraphs in length (Weiss, 2001b, 2003a, 2003b; Weiss and McMichael, 2004).

Haseltine was a very major AIDS researcher, and Weiss is surely among the foremost in the world. Yet the fallout from their efforts has been nil. What in the world is wrong?

Well, the fallout has not been nil, you say, because it has resulted in your piece here.

No, it has not. I first wrote about this idea in correspondence in September 1988, 23 years ago. I wrote not only about AIDS' transferring of new diseases, but that the AIDS population might provide an easily-infectable substrate within which incipient airborne or other casually transmissible HIV strains, currently unable to infect normal populations, could hone their skills. And I said at the time that these indirect effects of AIDS might well be more important then the well-known facts of its killing directly.

However, it was not possible to get such *un-orthodox* ideas published in 1988.

In 1992 I began writing down notes towards a paper, and in October 1993 I mailed off about 6000 words worth of notes to a prominent evolutionary biologist. Those notes contained the great majority of all the significant ideas about AIDS elaborated on in this piece.

In 1996-97 I attempted to write a long paper on the subject – 2/3 as long as this one – but gave up in despair of ever getting it published, shortly before completing the first draft in February 1997. From then until the end of March 2006, I simply gave up all work on AIDS and turned to other matters.

What prompted my return was the news I heard in February 2006 that bird flu had reached Africa. Before beginning this piece, I looked for evidence that others had already written about the idea, but found only the references to Webster. It was not until I was nearing the end of the first draft that I happened across one of the mentions by Weiss, quite by accident.

Perhaps, now, with the idea having been so strongly and repeatedly broached by one of the most prominent mainstream researchers, in major journals such as *Nature*, I will be able to get these ideas published. But it might have been helpful if one of the two most important ideas about AIDS had been known to all AIDS researchers 23 years ago, just as the other most important idea was known to all.

There is a significant further element to this story that I may, perhaps, write about at a future date.

13.1. A surprise ending

I am leaving the preceding discussion just as I originally wrote it [42], with the several modifications that are now needed given below:

After finishing all the drafts, and in the process of preparing the result for final submission, I ran across in my notes mentions of two papers I had meant to read but had overlooked. I read them. They were not significant enough to go back and include. But one of them mentioned a paper by Antia et al. (2003) which sounded important. I looked it up, and it was important, in providing a more complex mathematical treatment of the point about large enough transfers of pathogens that are not sufficiently transmissible to start epidemics resulting in enough chance passages to bring transmissibility over 1.0. It also had several other parallels to parts of my discussion, notably in its comments about monkeypox and falling herd immunity. But what really got my attention was the following paragraph from p. 659 (whose reference numbers belong to Antia et al.):

> The emergence of a disease combines two elements: the introduction of the pathogen into the human population and its subsequent spread and maintenance within the population. Ecological factors such as human behaviour can influence both of these elements, and consequently ecology has been recognized to have an important role in the emergence of disease[1,2,4]. In contrast, evolutionary factors including the adaptation of the pathogen to growth within humans and the subsequent transmission of the pathogen between humans are mostly considered in terms of changes in the virulence of the pathogen, and are often thought to have a lesser role in the initial emergence of pathogens[4]. One exception[5] suggests that immunocompromised individuals might provide "stepping stones" for the evolution of pathogens.

It was certainly interesting to find another expression of "my" idea (the author even used the term "stepping stones"), but the most interesting part was the very early date. It had appeared in *American Naturalist* in April 1989 (Wallace, 1989). And when I read the piece itself, I saw it had been submitted on 25 March 1988, six months before my letter. It was a short and very preliminary treatment, not even as detailed as that of Weiss, but the idea was clearly and unmistakably put forward, in a well-regarded publication, more than 22 years ago.

I searched through two citation indexes (Google Scholar and Web of Knowledge) and found only 6 papers that had cited Wallace in all those years. (Web of Knowledge had all 6; Scholar was missing one; but in addition there were two separate indexing errors, one by each index, so that their accuracy and completeness are in some question.) Clearly it is possible there were other citations I did not find, but I think the number must surely be minimal, and their importance likewise, or I would have learned of them through other avenues, and much earlier.

None of those 6 papers citing Wallace had any significant discussion or elaboration of his idea, despite the fact his paper had called on the biological community (and specifically and pointedly *not* the medical community) to evaluate this theoretical idea's practical importance. Contrary to my previous belief, the idea had been clearly put forward many years ago, at an early stage of the AIDS epidemic, in a respected scientific venue, yet no good had come from it. The first clear expression of the very serious danger is still the 2001 paper of Weiss, who has no mention of Wallace and who, I strongly suspect, like me, was completely unaware of him. And no good came of the five papers by Weiss, either.

There is a terrible, terrible tendency existing within science as it is currently constituted, which makes it almost more of a religion, or at any rate a culture, and a means of making a living, than a proper inquiry after truth. Ideas which go against the grain are stifled, firstly by being denied publication by the powers that be, but then by being dismissed or ignored if they somehow make it into publication despite this first obstacle. Wallace's idea made it into publication in time to have a significant effect on the world; yet the world squandered the opportunity, and now as (if?) my piece goes into print we have a very real chance of losing 1/7 or more of the world to a flu pandemic within the next couple of years, to say nothing of the other, potentially worse plagues looming perhaps only a decade or two further off in our future.

The internet has dealt a heavy blow to those powers that be that have prevented so much original and important work from being published over the years. But when the work manages to get published anyway, in a mainstream journal, only to be ignored, then it is clear the powers that be are just a reflection and a manifestation of a far deeper problem in science and in human culture.

It is a problem we shall dearly pay for. And one our children, and their children, shall likely continue to pay for as long as the human race exists, even if our generation promptly and completely corrects the problem now. But how can we correct it, when it is so deeply ingrained in all of us? How can a blind man will himself to see [43]?

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Some of these references include links. If in the future a link should cease to be valid, try copying and pasting the entire link into the search window of the Internet Archive's Wayback Machine (http://www.archive.org). The Internet Archive captures and preserves snapshots of billions of web pages as they existed on various dates in the past. Not all sites are indexed, but there is a significant chance of finding what you are looking for. Be aware that links are case sensitive.

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Notes

[1] The Encyclopaedia Britannica (1997, p. 987) estimates 21.5 million soldiers and civilians killed on both sides during World War I. A widely-cited recent estimate for flu deaths is 50 to 100 million (Johnson and Mueller, 2002). According to Barry (2004, p. 397), although the flu deaths occurred over a two-year period, most came "in a horrendous twelve weeks in the fall of 1918."

[2] According to Michelmore (1964, p. 67), a female salmon lays 30 million eggs. She doesn't say how many of these are fertilized, but I suspect (and can give reasons why) at least several million are. There are many more examples, including some very common ones from the plant world, such as trees, whose seeds, over a span of years, surely number in the millions. Especially in the plant world, there are numerous species which are self-fertilizing. Even though these species may be sexual, for obvious reasons, each will average only one surviving offspring, the principle being that each reproducing entity must average one replacement entity of the same sort. Thus in normal sexual species, each female averages one female, which translates into two offspring, but in species with seriously-skewed sex ratios, or other reproductive oddities, the number of offspring may be very different. Each queen honeybee may give rise to many thousands of offspring, but, on average, only one of them will be a queen bee who survives long enough to reproduce.

[3] This is the inevitable outcome of evolution acting in a state of nature. Of all the millions of species on our planet only one, we human beings, have the power, through laws impacting on all of society, to change the natural balance of reproductive rewards and punishments in such a way as to escape this trap. (Garrett Hardin (1968) had a memorable phrase for it: "mutual coercion, mutually agreed upon.") Unfortunately, it very much appears we do not have sense enough to do it, not, at any rate, in time to make good our escape.

[4] Many of the physical mechanisms for strengthening individual immunity by removing pathogens from the body, such as diarrhea, vomiting, coughing, and runny nose, not only benefit the individual with the infection but also the germ itself, by greatly

assisting in its spread to new victims – indeed, this may be virtually the only way the pathogen spreads. When both the sick individual and the germ are being benefited by a behavior, there is strong evolutionary pressure to maintain the behavior and very little evolutionary pressure to eliminate it (though there will be some through its harm to close kin). Consequently, despite benefiting the individual immune system, this behavior actively harms the species immune system by promoting the spread of the microbe. Another important example occurs when antibiotics are overused. This may often be to the good of the immunity of the patient receiving the antibiotic, but it harms the species immune system by promoting the development of resistant microbes. Anything that benefits the individual while harming the species in the realm of infectious disease would qualify as an exception. One that could turn out to be quite major is the flight to uninfected locations that occurs when a deadly epidemic strikes, assisting the threatened individuals who run but also assisting the microbe in its spread throughout the species. There are several other major examples that will be discussed later in this piece, as well as a few more that I did not have room to include.

[5] Leonard Lopate Show, WNYC-FM, 9 January 2006, available for listening online or download of the MP3 file at http://www.wnyc.org, in the Leonard Lopate Show archives. I later read the book itself. Despite my criticism of the author's apparent position regarding quarantining (more prominent in the interview than the book), I thought the book was impressively well done, certainly when viewed as a social history. For the last several decades there has been very good treatment for leprosy, which renders quarantine no longer necessary; but there was no effective treatment during the great majority of the Molokai colony's existence. Leprosy victims find the word "leper" *highly* objectionable, a fact I had not been aware of, and consequently I have rephrased several passages to avoid the word.

[6] If each person infects 1.1 others, it requires 7.2725 generations to double. 40 x 7.2725 = 291 generations to increase a trillion-fold. In 200 generations, it would increase 190 million-fold; and while this is absurd for leprosy and most diseases, flu can do it.

[7] I could not find any estimates of the number of extra tuberculosis deaths to non-HIV-infected people as a result of the AIDS epidemic, but the following gives some indication: According to Corbett et al. (2003, p. 1014), in the year 2000 1.4 percent of all TB transmission events were directly due to HIV (for Africa the figure was 7.5 percent), meaning the person doing the transmitting had HIV and would not have been likely to have had a transmissible case of TB without the HIV. It understates the true effect of HIV, since those non-HIV-infected individuals who caught their TB as a result of these transmissions will also transmit it on, and these cases (and their progeny) are also a result of HIV, but are not being counted as such. The 1.4 percentage can be expected to grow so long as the fraction of the population with AIDS continues to grow, and that has already increased appreciably since 2000. There are complications to figuring out the number of extra deaths, but when 1.8 million people are dying in the world of TB every year, and only 246 thousand of these deaths are to people with HIV (Corbett et al., 2003), it is reasonably clear that we are talking about thousands of extra TB deaths every year to non-HIV-infected people as a result of HIV. Though the numbers are very approximate, it appears that somewhere on the order of as many non-HIV-infected people have died as a result of AIDS-fueled TB as have died of AIDS caught from transfusions, and that is a number large enough to

have claimed two major celebrities, Arthur Ashe and Isaac Asimov. Moreover, the annual numbers of the TB-caused deaths are still rising, while transfusion AIDS deaths worldwide are likely well past their peak annual incidence. In the poor nations, AIDS patients die much less frequently of opportunistic infections that healthy persons don't have to worry about catching, and much more often from pneumococcal pneumonia, salmonella, and TB (and possibly malaria), which are high-grade pathogens that threaten everyone (Maher et al., 2002, p. 11). Tuberculosis is the biggest single cause of death of AIDS patients in many poor nations.

[8] Ebola, Lassa, Marburg, Nipah, Andes virus, maedi (the 100-percent-fatal airborne lentiviral lung infection that almost wiped out Iceland's sheep industry in the 1930s and '40s, stopped only by slaughtering every sheep in the half of the country to which the rapidly advancing disease had spread), equine infectious anemia virus (the less-than-100-percent-fatal close relative of maedi that reportedly infected several humans in the 1920s (Montagnier et al., 1984)), feline immunodeficiency virus (an increasingly common fatal lentivirus infecting pet cats), simian hemorrhagic fever, the many immunodeficiency viruses of monkeys and apes (not only the SIVs but the SRVs, non-lentiviral type D retroviruses that caused immunodeficiency epidemics in primate centers in the mid-1970s (Gardner, 1996)), no doubt many more diseases that experts will be able to name, and no doubt many more that no expert can name because no one yet knows of their existence: they may not have been discovered because they exist in little-studied species in remote locations, or, as in the case of HIV itself, they may never have been noticed because they do not cause sickness in the species they ordinarily inhabit (even when, as in the case of one SIV, they are among the commonest infections of one of the most intensively laboratory-investigated species on the planet, the African green monkey, and its better-known subspecies, the vervet).

[9] A 25 mg injection of cortisone acetate is a medium-sized dose for an adult human being, with 12.5-25 mg being recommended for Addison's disease (chronic failure of the adrenal glands to produce cortisol). A typical adult human being weighs about 1000 times as much as a 1-day old duckling (assuming the duckling weighs about as much as a good-sized hen's egg), so that an equivalent dose for an adult human being would be 25 grams, or just under one ounce.

[10] At least one of the Indonesian cases was human-to-human-to-human, and so should not be counted in figuring the chance of bird-to-human-to-human passage.

[11] Usually it takes significantly more than 6 or 7 passages. However, there is an important difference between these artificial passages and the natural ones that occur as a pathogen attempts to adapt to a new species. The deliberate, artificial transfers are selecting for ability to grow fastest within the individuals the pathogen is transferred into, without the pathogen having to divert any resources at all towards spread to additional individuals. The experimenters will go out of their way to *force* further transfers, with huge doses and especially-susceptible subjects, and the transferred organisms only have to survive and grow as well as possible within whatever individuals they are placed in. The natural transfers, on the other hand, such as occur when humans get bird flu, are directly selecting for ability to transmit an infection to other individuals when it is already able to grow within individuals if artificially placed there. The deliberate transfers, by tending to increase the titers of the pathogen, as well as the range of organs it can grow in, will probably also increase

transmissibility. But this transmissibility increase is indirect and uncertain. Selecting directly for transmissibility, as occurs with the natural bird-to-human and human-to-human spread of bird flu, will be more efficient, and will produce a strain whose transmissibility is greater than 1.0 with fewer individual-to-individual passages than the artificial transfers will require. The difference is likely to be substantial. Indeed, the artificial transfers can easily reduce transmissibility, as can be seen in examples of direct brain-to-brain transmission, which could change an already-transmissible respiratory pathogen into one able to grow only within the nervous system. Such a pathogen would ordinarily lack any means of spread to the nervous system of other individuals, except through further deliberate transfers.

In other words, it might be possible to deliberately adapt bird flu to humans faster in time by artificially transferring it from human to human to human, until it became transmissible enough to sustain itself. But though natural transfers might take longer in time to produce a self-sustaining strain, or might fail to ever produce one, if self-sustainability eventually does occur, it will likely have taken place through a significantly shorter chain of passages.

[12] Assume there are B cases caught directly from birds and that the transmissibility to humans of these initial cases is r. Then the first human-to-human passage will consist of Br individuals. If r remained constant, then the second passage would consist of r times the first passage, or Br^2, but r itself increases by a factor c with each additional passage, because the microbe is becoming more efficient at colonizing its new environment as evolution selects the most successful variants. Assume that c is constant for each succeeding human-to-human passage, at least until transmissibility reaches 1.0 after p human-to-human passages. Thus the numbers in the second passage are $Brrc$, or Br^2c; in the third, Br^2crc^2, or Br^3c^{1+2}; and in the fourth, $Br^3c^{1+2}rc^3$, or Br^4c^{1+2+3}.

Each succeeding generation of human-to-human passage will consist of smaller numbers, until transmissibility reaches 1.0 in the pth passage, after which, as transmissibility surpasses 1.0, numbers will begin to rise. The number of cases in this smallest generation is therefore $Br^pc^{1+2+3+\ldots+(p-1)}$. But the sum of integers from 1 to $p-1$ is given by the well-known formula $S=p(p-1)/2$. Therefore the size of the minimum generation simplifies to

$$Br^pc^{p(p-1)/2}. \qquad (1)$$

Now c is the constant factor that carries transmissibility from r to 1.0 in $p-1$ steps (the first human-to-human passage is Br, then there are $p-1$ more in going from r to 1.0). The transmissibility for the pth human-to-human passage is therefore rc^{p-1}, and since by hypothesis this is equal to 1.0, we can see that c is the $p-1$ root of $1/r$, which can be written as $c=r^{-1/(p-1)}$. Substituting this value for c in equation (1) for the size of the minimum generation of human-to-human spread, therefore gives $Br^p[r^{-1/(p-1)}]^{p(p-1)/2}$, which equals $Br^pr^{-p/2}$, and this, finally, is $Br^{p/2}$.

[13] I write this note as a suggestion for further research by others and to point out several pitfalls they should avoid.

There were two important errors of my own in my Version 1 and 2 account of *C. difficile*. First, I unconsciously assumed the apparently greater toxin production of the PCR ribotype 027 strain had come about in response to a recent environmental change (which I argued was its recent entry into humans). I had not eliminated the

possibility that this particular strain had produced more toxin all along. Second, I argued that greater toxin production in response to its recent entry into human beings, in order to produce greater diarrhea, in order to more efficiently spread itself around, made good sense, while other alternatives were possible but farfetched. I later thought of an alternative that was not farfetched: An ancient human pathogen exposed to the new environment of antibiotics might have evolved greater toxin production in order to produce more diarrhea in order to dilute the noxious antibiotics it was now having to combat. It was sort of an all-purpose antibiotic resistance strategy for intestinal microbes.

But there were other problems caused by shortcomings and contradictions in the literature itself, which my limited reading did not detect. I relied heavily on one paper (Warny et al., 2005) for my information that PCR ribotype 027 produced more toxin. They compared toxin production by the 027 strain with some other strains, and concluded that the 027 strain produced about 20 times as much of the two principal toxins, called toxin A and toxin B. However, they tested toxin production *in vitro,* while Åkerlund et al. (2006) found no relation between levels of toxin production *in vitro* and *in vivo.* Even studies *in vivo* are problematic, because diet significantly influences toxin production. At least in germ-free mice, a change of diet can cause a 100-fold change in toxin production (Åkerlund et al., 2006, p. 357).

Moreover, they measured the amount of toxin by its *weight.* This was inadequate because Stabler et al. (2009, Table 2) have shown that slight molecular differences in the toxins produced by different strains can cause enormous differences in their toxicity – up to at least 7500-fold. Thus a 20-fold difference in weight is insignificant.

Stabler et al., as well as others, have measured toxicity by the dose necessary to kill various cells in culture. This is better, but one cell type may be thousands of times as sensitive to the toxins as another, and one gets very different results depending on which cells are used. Thus, Table 2 of Stabler et al. (2009) shows toxin B from *C. difficile* strain R20291 is 56.25 times as potent as the same weight of toxin B from strain 630 when tested against MDCK cells. But if the same strains are tested against HeLa cells, then strain R20291 is 7500 times as potent. Table 2 of Stabler et al. tests toxin B from 3 strains against 8 different types of cells, and achieves consistent results as to which strain is most and least toxic. Two of the strains are the 027 type, and in every test the more recent strain is more toxic than the earlier one, giving at least a little bit of evidence that 027's toxicity has been rapidly increasing. However, even though I strongly suspect it is true, many more 027 strains would have to be tested in order to be able to make a case for this claim.

Another problem is that most researchers have gauged toxicity by looking only at toxins A and B, while the 027 variety, as well as a few others, are unusual in also having a third toxin, called binary toxin. Most researchers have regarded binary toxin as being of lesser significance, but it has not been well studied, and if its toxicity also varies by thousands of fold, it might be highly significant in those strains with the most toxic versions – if not now, then as it continues to evolve in the future.

The paper by Warny et al. was published in *Lancet* and attracted much attention in both the popular and scientific media. A few people pointed out some of the above problems (Freeman et al., 2006; see also the reply by Warny et al. immediately after), but several of them I had to find on my own. In general the paper was very well received and is still cited favorably. I do not mean to single it out as especially bad,

since many other researchers have made similar errors. Rather, by singling out the errors, I hope to prevent at least some of them in the future.

Another pitfall that could explain some of the contradictory results researchers have reported regarding whether or not the "super" strain, PCR ribotype 027, is in fact more virulent (most say yes; some say no), is that some 027 strains may be super strains and some may not be. Any favorable *C. difficile* variation can (in theory) be traced back to its first occurrence in a single bacterial cell in a single host's body (or wherever it lives), from which place and time its spread began. It may ultimately crowd out all the bacteria of the same strain that lack the variation, but this will take time, and meanwhile the ordinary, now inferior, members of the strain will go on infecting others. The "super" type of 027 may well not yet have displaced all the ordinary 027s, and researchers who do not realize that the various 027s are very different from one another will claim contradictory results. This variation is to be expected if I am correct in my strong suspicion that 027 has only *recently* become a super strain (and that it will continue to get worse, and that other super strains will independently emerge, as they continue to adapt to what is likely to have been quite a recent, and ongoing, transfer into our species).

My claim at the beginning of this note that antibiotic exposure could have caused *C. difficile* to become more virulent, in order to produce more diarrhea, in order to dilute the antibiotics, needs more work. Metronidazole, the commonest antibiotic used to treat *C. difficile*, behaves in precisely the opposite way: it is so rapidly absorbed by the small intestine that almost none remains to reach the *C. difficile*, whose home is in the large intestine, unless it is rushed through the small intestine by diarrhea (DuPont et al., 2008). I think metronidazole is anomalous (certainly vancomycin does not behave that way), but in fact I have not investigated how the other chief antibiotics *C. difficile* has been exposed to behave or whether any old human intestinal pathogens have produced increased diarrhea in response to the advent of antibiotics.

My claim that PCR ribotype 078 may have transferred to us, or be in the process of transferring, from antibiotic-treated farm animals, has an interesting alternative that is worth considering. Inasmuch as both we and the animals have been heavily exposed to antibiotics, perhaps 078 entered first through us and we gave it to the animals. (And now we are catching it from them as well as from each other.) Human-to-animal transfer may seem much less likely, in view of the fact that humans eat animals a whole lot more often than animals eat humans, until it is realized that in some parts of the world pigs are fed human feces (Miller, 1990; Sarti et al., 1992), and our feces is where the *C. difficile* is. It is also possible 078 was acquired independently from some other source by both us and farm animals, once antibiotics had turned us both into growth media in which it could maintain itself.

A very important question that I think current research has not answered is whether *C. difficile* solely, or almost solely, lives within the intestinal tracts of animals, with spores found in the outside world merely due to contamination from animal feces. This might be quite a good thing, if true, for it would imply that any new human *C. difficile* strains were already adapted to the intestines of other animals and therefore already partially adapted to our own intestines, with significantly less room for further improvement than would be the case for an organism whose natural home was soil or water or some other part of the external environment. I think it should be fairly easy for researchers to find *C. difficile* living and growing in the external

environment, if in fact it does so.

A final very important question that I have not seen investigated is whether in those cases where *C. difficile* causes symptomatic infections in individuals who have not had any recent antibiotic treatment, their colonic flora was more-or-less intact or whether *C. difficile* was only able to attack individuals whose flora, for some other reason, was disturbed.

[14] I ignore the other varieties not because they are not significant but because they are a needless complication to the points I am trying to make. Though HIV-1 group M may currently have the vast majority of infections, all of these varieties are rapidly adapting to the human species, becoming more transmissible with every generation of spread, as the most transmissible variants disproportionately succeed in infecting the next generation of victims. The degree of adaptation the various types ultimately achieve may bear little relation to their current degree. Whether HIV-1 group M will still be the worst variety 100 or 200 years from now is very much an open question.

[15] Comparing the amino acid composition of the HIV-1 group M *tat* gene protein, Korber et al. (2001, p. 33) found up to 42 percent differences, and they only looked at 12 subtype A and 37 subtype B sequences out of the millions that exist in the world, or tens of millions if the other subtypes are included. Since all the various subtypes are roughly equidistant from each other, it is possible all the world's infections don't include a substantially greater genetic distance; however, their various A vs B comparisons ranged from 27 to 42 percent, indicating to me that a larger sample size would have made more than a negligible difference. Moreover, this was the state of things in 1999, while the divergence has continued to grow in the years since. And even 27 percent would be chilling. Indeed, I would argue that the 27 percent minimum divergence is a more chilling statistic than the 42 percent maximum.

[16] The incipient infection might actually be more likely to transfer if the transmissibility is below 1.0 in AIDS patients to start with. If it is too high, or increases too rapidly, all the susceptibles will become infected quickly, within a relatively few human-to-human passages, and the new organism will die out for want of anyone left to infect that it is by that point able to infect. (Though this is not entirely clear in AIDS patients, whose impaired immunity may leave them susceptible to reinfection.) On the other hand, efforts to contain the disease will if successful reduce its transmission, but may well not stop it, since the more successful these efforts are, the less will be the pressure to keep them up. In that way, even very transmissible diseases may manage to keep going indefinitely in AIDS patients. This is somewhat similar to the leprosy example, where enough pressure is applied to a disease with a rather high potential transmissibility to hold cases to an acceptable level and reduce transmissibility to 1.0 (a level that will often be sustainable indefinitely).

[17] Paul Ehrlich, in several of his books about overpopulation (e.g., Ehrlich, 1971, pp. 47, 62-72) writes about potential new diseases such as Marburg virus and Lassa fever starting as a result of overpopulation. However, one difference in my account which I have not seen elsewhere is the point that brand new pathogens that enter because of overpopulation and are around long enough to adapt well to our species may well remain as human pathogens even if they cause the predicted worldwide plagues that remove the overpopulation that let them in in the first place. Just as removing AIDS will not eliminate those new diseases that have outgrown their dependence on it, neither will removing overpopulation. However, the rapidly-spreading plagues, such

as in fact Marburg or Lassa would be, might need large surviving populations just to keep them always circulating. The slower-acting or persistent diseases, those like AIDS or TB or malaria, would be the ones most apt to survive even with a greatly reduced human population size.

[18] Unless maybe by giving the xenotransplant to an AIDS patient: see Altman (1995).

[19] We know it doesn't escape the great majority of the time, for otherwise we would already be overrun with new diseases. Despite the fact that vCJD (the human version of mad-cow disease) is only a few years old and only about 200 people are known to have gotten it, there are already four known cases of transfer of vCJD via transfusion (Health Protection Agency, 2007), and this is not a disease that spreads easily through blood. The total number incubating vCJD has been estimated from surgically removed samples to be about 4000, assuming no cases were missed (Gregori et al., 2006). This is a highly optimistic assumption and implies that less than 5 percent of the vCJD cases have yet shown symptoms. Since the four transfers via transfusion, three of which were symptomatic, have had less time to develop symptoms than those infected through consuming tainted meat, it is reasonable to estimate that perhaps 60, or perhaps several times that many, transfusion-associated cases have in fact already occurred, but that the years-long incubation period has so far passed for only a handful. The years-long incubation period also means some of the transfusion-associated cases not yet showing symptoms would likely pass it on through further transfusions, adding another link to the chain, except that because of vCJD in 2004 the U.K. banned all recipients of blood transfusions since 1980 from donating blood.

[20] In a medical injection essentially no blood goes up into the needle, because the needle is full of fluid from the tiny amount of liquid that is ordinarily squirted out to remove the air bubbles. Even if this is not done, the small amount of blood, going partway up the needle only, will be washed back out when the injection is given. The blood clinging to the outside of the needle will surely be a small fraction of a cubic millimeter. There are a million cubic millimeters (one one-thousandth of a cubic centimeter) in a liter of blood. Illegal drug injectors, on the other hand, frequently employ a practice called "booting," in which they purposely suck some of their blood back into the syringe, then squirt it back into their bodies, then suck some more, generally repeating the process several times, before injecting the bulk of the drug. This might well result in hundreds or thousands of times as much blood being transferred if the same needle and syringe are used by another drug injector, compared to the amount transferred by the medical reuse of nonsterile needles.

[21] Anyone looking into this matter has some work to do. The official sources have been so biased against the theory, refusing to publish much of the best evidence in its favor, that considerable auxiliary reading is necessary. The best place to begin is the website of Brian Martin at the University of Wollongong (http://www.uow.edu.au/~/bmartin/dissent/documents/AIDS/), which contains a large compilation of writings by many authors in support of the theory, as well as a few key writings and some hard-to-obtain documents from the other side, such as the Wistar Committee Report of 1992 (Basilico et al., 1992). The three papers by Louis Pascal (1991, 1993, 1994), the original author of the theory, are particularly important. Also not to be missed is the very angry letter by W.D. Hamilton to *Science* editor-in-chief Daniel Koshland, protesting the rejection of Hamilton's letter to *Science* pointing out deficiencies in a piece they had published opposing the polio theory

(http://www.uow.edu.au/~/bmartin/dissent/documents/AIDS/Hamilton94/Ham940223.html). Hamilton pointed out 12 errors in the short piece opposing the theory, yet his letter was rejected by *Science* without any attempt to answer any of the 12. Despite this remarkable letter to Koshland, the publication would not back down. No correction was ever made, no hint to its readers that anyone had questioned the published piece's accuracy, let alone the fact that the man many regarded as the foremost evolutionary biologist in the world had pointed out 12 errors.

One should then turn to the massive book, *The River*, by Edward Hooper (2000), who spent years looking into the question. Hooper found evidence (though not proof) that chimpanzees had actually been used to make the polio vaccine in question. This has been hotly disputed by the vaccine makers, who, however, have no better evidence of what they actually used than does Hooper. Hooper worked closely with Hamilton, and indeed Hamilton wrote the striking introduction to the book. There is also a great deal of important material on Hooper's website (http://www.aidsorigins.com).

There have been two conferences of note that discussed the question. The impetus for both conferences was again due to W.D. Hamilton. The first was a 2000 conference at the Royal Society, whose papers are published in vol. 356 of *Philosophical Transactions of the Royal Society of London B,* 2001. The second was a similar conference held one year later in Italy, at Accademia Nazionale dei Lincei. Its papers are published in vol. 187 of *Atti dei Convegni Lincei,* 2003. Several of them are available on the websites of Martin or Hooper.

Hamilton, a strong supporter of the theory, was originally slated to be co-chair of the Royal Society conference. Robin Weiss, an opponent, was also co-chair. Tragically, Hamilton died two months before the scheduled date of the conference, leaving it largely in the hands of the theory's opponents. The result reflected this.

Finally, the excellent book by Bookchin and Schumacher (2004), though primarily about SV40, and containing not a word about HIV's possible origin, includes so much useful information about the early polio vaccines and the shenanigans that accompanied them, as well as the powerful efforts to suppress not only public but scientific knowledge of SV40's role in human cancers, that it is an important addition to this documentation.

Since 1992, claims that the theory has been refuted have been repeatedly announced in the establishment media. All of these claims have collapsed upon even modest scrutiny, and several have turned out to be points for the other side. The contaminated oral polio vaccine theory of AIDS' origin may not have been finally proven, but it has certainly not been refuted.

[22] This is discussed at length in Bookchin and Schumacher (2004, pp. 206-216), which shows that SV40 inhibits several important human anticancer mechanisms, including the p53 gene and all three retinoblastoma proteins, accelerates cell growth in two separate ways, acts on telomeres to allow cells to divide indefinitely, and stimulates the growth of blood vessels into the tumors once they are formed. Key references given there are to Carbone et al. (1997), De Luca et al. (1997), Foddis et al. (2002), Cacciotti et al. (2001), Cacciotti et al. (2002), Bocchetta et al. (2003).

[23] According to the World Health Organization, setting standards in 1975 for yellow fever vaccine, "The Committee agreed that, until it was possible for the majority of manufacturers to obtain a source of eggs free from avian leucosis viruses (ALV), requirements demanding freedom from these extraneous agents could not be written

since they might reduce the availability of vaccine and create an unacceptable public health risk" (WHO Expert Committee on Biological Standardization, 1976, p. 18). "The use of yellow fever vaccine for more than 30 years prepared from the 17D strain now known to contain avian leucosis viruses, has not been shown to be associated with untoward long-term reactions" (ibid, p. 26). Twenty years later, at its forty-sixth meeting, the same committee revised its yellow fever vaccine requirements somewhat, however "the revised Requirements do not specify ALV-free eggs." Although the meeting was held in October 1995, WHO did not publish the report until 1998. Consequently, at least as late as 1998, avian leukosis virus was still permitted in yellow fever vaccine (WHO Expert Committee on Biological Standardization, 1998, p. 33). I find it hard to believe that this is still going on, but if there has been any later addendum prohibiting avian leukosis, I have been unable to find it. Influenza vaccines were also contaminated with avian leukosis in the past (Coriell, 1968, p. 185). However, I have not taken time to research contamination of this vaccine and do not know the extent of the problem.

[24] One could, for example, assign the four DNA bases, A, C, G, and T, to the four binary numbers 00, 01, 10, and 11. A sequence of four of the bases can then be used to represent the first 256 binary numbers, from 00000000 (AAAA) to 11111111 (TTTT), and these can represent 256 different characters, which a computer can display, the most obvious assignment probably being to simply duplicate the 256-character ASCII code already so widely used in computers.

[25] In just a few minutes of thinking I came up with four methods for enabling a new organism to spread, at least one of which would definitely work. I first wrote that I did not intend to tell any of them, but when I read Gurian-Sherman and Lindow (1993, pp. 1339-40), I saw that one of the other three methods appears already to be being used, though evidently with no awareness of the potential for creating lifeforms able to outcompete and potentially eliminate the natural versions, and able to evolve in new and unexpected directions. Therefore, by mentioning it I am hopefully doing more to reduce the danger (if practitioners can be made to see what they are doing) than to add to it by explaining how such a thing can be done. Gurian-Sherman and Lindow describe a sensitive test for determining if the new gene a bioengineer is trying to insert into an organism has indeed been inserted and is functioning. It is a simple means of attaching the small ice-nucleation gene to the gene one wants to insert. One then grows the results for long enough for the gene, if it was successfully inserted, to produce some ice nuclei. One then measures how efficiently tiny droplets are converted to ice at various temperatures. The ice-nucleation gene makes a dramatic enough difference that even very small numbers of successfully-inserted genes can be detected in this way, much smaller numbers than were possible in previous methods of testing. Moreover, unlike many genes, the ice-nucleation gene uses only tiny amounts of metabolic resources, so that its presence is likely not to cause any noticeable degree of interference with the gene one is actually interested in. Because the ice nucleation gene uses so few resources, it is also not likely on that basis to materially decrease the fitness of the organism it has newly been placed in. But, depending on the organism and its ecology, it may greatly increase its fitness by adding ice nucleation to its repertoire. If this fitness addition is greater than the likely fitness subtraction due to the other gene added at the same time, then the combination will be more fit than the original, and should spread, even in the wild. The fact that the two genes are so closely

connected will make it much harder for the organism to eliminate the presumed detrimental addition while keeping the favorable one. And if both are kept for a long enough time, evolution will find ways to reduce the detrimental effects of the one and increase the positive effects of the other, with the end result being that occasionally one or two offspring will come into existence before the last instance of the detrimental gene has been eliminated which will have both of the new additions now producing positive fitness changes. In that case this new variant will be able to outcompete its relatives, and both new genes may persist indefinitely. Ice nucleation is currently quite a rare trait in nature, and there is evidence that most of the few species that possess it may not have evolved it themselves. Rather, their possession may be due to occasional chance occurrences of natural gene transfer from one bacterial species into another (Edwards et al., 1994). Ice nucleation may have evolved only once or a very few times in nature, but been found to be useful enough for it to have spread into organisms that did not evolve it. If this is so, it is not an easy thing to evolve. Should ice nucleation become far commoner among organisms due to these experiments, there would seem to be a significant potential for it to produce large-scale changes in the world.

[26] Please note that Greger's ideas about immune-deficient chickens allowing a virus from another species to become a chicken virus, able after adaptation to these susceptible stepping-stones to infect and persist in non-factory-farmed chickens and even in wild waterfowl (I don't think he says whether in the waterfowl it remains able to spread as a respiratory virus or reverts to being fecal-oral, but this would certainly be interesting to know), is precisely analogous for the chickens to my ideas about immune-deficient humans enabling new pathogens to infect the population at large. And if our chicken creations do remain as respiratory viruses after reinfecting waterfowl, it is very nearly analogous to my arguments later in Section 9 about how immunodeficiency can lead to the emergence of evolutionary potentials that are otherwise kept suppressed. There is one extra step, passage through the chickens; but surely it is likely that if ducks or geese were kept under the same conditions as chickens, their fecal-oral virus would also change into a respiratory one; and if it were able to persist as a respiratory virus even among wild birds, this would then be precisely analogous to my arguments in Section 9.

[27] Under some circumstances it might be possible for new potentialities to evolve during a natural period of rapid spread of a disease, for example when it encounters a virgin population as many diseases did when the Old World first contacted the New, since again the struggle for existence is relaxed and temporarily less fit strains may now have enough time to evolve into more fit strains, or into divergent strains that compete less directly with the original. I do not know whether this has ever occurred. Visna, arising from the virgin-soil outbreak of maedi in Icelandic sheep, seems a likely candidate. And though it is anything but natural, the factory-farm-bred evolution of mild fecal-oral bird flu into a killer virus spread by the respiratory route clearly shows how great is the evolutionary potential and what striking changes in disease characteristics and propagation methods and host species can occur in short time frames when potentialities that are normally suppressed become able to survive and adapt (see Section 8.6.3).

[28] For cases such as transfusion, it is actually more like a log has fallen across a chasm, allowing it to be crossed, since no downward movement is required.

[29] And it may have done this already, possibly more than once. Perhaps the original virus, when first transferred from chimpanzees, was too ill-adapted to its new environment to spread in any way less intimate than transfusion. But suppose it got enough free transfers thereby to enable it to adapt well enough to spread via shared illegal drug needles and/or anal sex. After more generations of adaptation in these populations, it became well enough adapted to be able to spread efficiently via regular, vaginal, heterosexual sex, expanding the size of its risk group with each new advance. What then might be next?

[30] "Serum from a Haitian patient enhanced the ability of three different isolates of HIV to infect cells, whereas serum from an American patient neutralized two of the isolates and enhanced infection with the third" (Barnes, 1988). See also Kliks et al., 1993.

[31] Of 18 AIDS patients undergoing broncho-alveolar lavage because of lung problems (when presumably the immune deficiency was significant), one had 6.3 times the normal number of alveolar macrophages, and other patients had lesser degrees of elevation (Pearce et al., 1993, Table 1, p. 724). Since macrophages, not lymphocytes, are the usual targets of newly-transferred HIV virions, a good case can be made that this likely increased susceptibility extends throughout the infection, or at the least potentially extends throughout the infection, awaiting only the evolution of a strain that can exploit this promising new niche.

[32] Much of the case for airborne spread was put together by John Seale a long time ago (Seale, 1985, 1986). I contributed the evolutionary aspects and the ominous potential provided by other immune-deficient individuals.

[33] There is much uncertainty in the total deaths due to World War II. I have chosen a round figure that is often given. The *Encyclopaedia Britannica* (1997, p. 1022) estimates 35-60 million.

[34] The UN estimates urbanization was 13 percent in 1900 and 29 percent in 1950 (UN Population Division, 2006, p. 1). A linear interpolation gives 18.8 percent for 1918.

[35] There is one *simple* step that can significantly reduce electricity demand society-wide; if taken quickly enough when the system comes under threat, it might suffice to save the power grid: Shut off power to or otherwise stop all television broadcasts. The power consumed by the broadcasters is trivial. The power consumed by the millions of television sets watching the broadcasts is immense. (I heard this idea many years ago, before there were DVDs and before VCRs were common, but the impact would still be substantial; I don't know whom to credit for it.)

[36] A similar idea which came to me after reading MacKellar is that we should also vaccinate pigs against human flu! I do not know whether a human flu vaccine would protect a pig, but surely it is worth a try, and surely if it does not work, it is worth a crash effort to develop such a vaccine. Incidentally, there are a number of different flu vaccines in use around the world for protection against conventional flu, and some of them are live virus vaccines. Those particular vaccines might themselves present a risk of recombination with bird flu.

[37] In the world's richest country, the U.S.A., there are about 1,000,000 hospital beds. This is equal to one-third of a percent of its population of 300,000,000. At any given time, most of these beds are occupied. The U.S. does not have 1,000,000 beds available for a flu epidemic, but only the empty beds. If 30 percent of its population (90 million people) falls sick over a 3-month time span, how many of them will fit into the few empty beds? And how many extra hours of leisure time does the average doctor have

available that could be turned to care for flu victims? Well, in an emergency, tents and schools will be used for hospitals, and soldiers and police will substitute for doctors, so some level of medical care will be available for more than these numbers would indicate. But it will be grossly inadequate. In a normal flu epidemic, few flu victims need hospitalization; but the great majority of bird-flu cases have desperately required *intense*, and often rather prolonged, hospital care.

[38] There was no factory farming in 1918, yet the 1918 flu came directly from a bird. It might have been a chicken, or perhaps a duck or goose. But just as virtually all the human cases of today's bird flu have had domestic poultry as their most immediate avian ancestor (as opposed to a wild bird), so also I regard it as extremely likely the first soldiers infected in 1918 caught it from domestic poultry. Barry (2004) and others have painted pictures of badly-crowded, highly-stressed, humans undergoing emergency training for World War I in America, and in even worse conditions in the trenches of Europe. These crowded and stressed soldiers might well have replaced crowded and stressed factory-farmed chickens as the stepping-stone that allowed a few rare flu infections caught from poultry to survive and adapt and intensify in virulence and transmissibility until the 1918 pandemic virus was born. There are advocates for specific encampments in Kansas, USA, and in France as the origination point of the 1918 flu. But if there was worldwide distribution of a flu virus in birds that under the right circumstances could adapt to humans, it seems to me this might have occurred, some fraction of the time, wherever it found those circumstances, and that looking for a single point of origin may be unnecessarily restrictive and may obscure an important insight into the process by which such events occur. (I am not favoring any of these three theories of where the 1918 flu began; it seems to me they are all tenable.)

[39] But suppose the lack of poultry resulting from such a law meant the yearly flu epidemics hardly ever happened anymore, causing our herd immunity to drastically fall, making each epidemic that did occur far worse? Under more normal circumstances I would want this possibility investigated by flu experts and disease modeling experts (though I have much distrust of these models), but in the current emergency situation there is no time for debate. It is reasonably clear such a law would drastically reduce the sporadic bird flu infections we are having today, thus drastically reducing the chances for a pandemic. Any significant decrement to the herd immunity would take many years to develop. After the law is passed and after the current horrendous form of bird flu has been replaced by a more normal one (as will happen after the law is passed and we stop making more of the killer strains), we can debate at our leisure whether such a law would do more harm than good if left in place during ordinary times, or whether, perhaps, we would be better off if factory farming alone were banned. My guess is that the yearly flu epidemics, which occurred every year even when China had one thousandth its current poultry population, would not be much impacted by the law, so that it should be left in place. The greatest killer epidemic in all history did not require factory farming, but likely did require domestic poultry. Never eating poultry or their eggs again seems a very small price to pay to avoid a disaster as large as World War II (indeed, if my billion-deaths estimate for bird flu is accurate, as large as 20 such wars). One may think this question is all beside the point, since such a law will never be passed in the first place. This is likely true, but the emergency is so great and can be so easily escaped through this measure, that even a small chance of passage is worth making a great effort to achieve. Besides, if it isn't

passed and a billion or two people die, the survivors will be a lot more likely to pass such a law in the second place, so that the question will need to be considered then.

[40] Fisher-Hoch (2004, see Fig. 20.5, p. 621) shows generations of Ebola cases running 1 case 1 death, 5 cases 4 deaths, 7 cases 6 deaths, 5 cases 5 deaths, 10 cases 5 deaths, 5 cases 1 death, 1 case 0 deaths. Up through 5 cases 5 deaths there is certainly no evident attenuation. Suddenly deaths fall to 50 percent, then 20 percent, then 0. What happened between generations 4 and 5? Perhaps the virus *suddenly* decided to attenuate. Or perhaps the exposure in the medical clinics, where most of the cases had been acquired, was reduced when it became clear what was happening. This could have affected mortality in two ways. Extra precautions might have meant that when the infection was transmitted, it was with a lower inoculum, and produced a less deadly illness. Or perhaps the route of exposure was different. Most of the hospital-borne cases arose via needle-stick exposure. If this was halted, then alternative routes of infection may have been less often lethal, either because lethality may vary depending on the initial site infected, or because fewer virus particles got in through the alternate route.

[41] What about closely-related non-offspring, such as in kin selection? There are some complications in this case (ignoring recombination, we are dealing with completely separate lineages, which might as well be completely separate species; and the closer they are, the more direct the competition), but I am not sure how relevant they are. In any event the question is too far afield to worry about here.

[42] This was true for the first version, but the greater length and later date of the current version have required small changes: The unpublished paper I described as "5/6 as long as this one" has been changed to read "2/3 as long..."; Haseltine's article in the *New York Times* of "more than 16 years ago" is now changed to "almost 19 years ago"; the two references to my correspondence from 1988 have been changed from "21 years ago" to "23 years ago"; and because of all the non-AIDS material added in the two later versions, the sentence "Apart from the material on the flu, those notes contain the great majority of all the significant ideas elaborated on in this piece," has been changed to read "Those notes contained the great majority of all the significant ideas about AIDS elaborated on in this piece."

[43] I do have some significant thoughts on how this problem might be substantially reduced, but they will have to wait. Suffice it to say that a large part of why we are blind is that we have willed ourselves not to see. And we have willed ourselves not to see, at least in part, because of the balance of rewards and punishments. And this balance it is in society's power to change, at least if society can be brought to understand that its very survival is at stake. And this is a lesson that can be learned the hard way, if (as I fear) we prove unable to learn it otherwise. The question then becomes whether we will learn it only after it is too late. And the answer may depend more than anything else on two purely chance matters: on exactly how soon the first of the predicted plagues comes about, and on exactly how bad it is.